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STUDIES ON MALIGNANT HEPATITIS

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In recent years an increasing interest in hepatic diseases is manifest all over the world; this applies to both the acute and chronic forms. It is at least partly due to the violent outbreaks of infectious hepatitis observed during the war in many countries such as the epidemics among troops in the Middle East[1,5,7,9] and in the Pacific,[12] in London,[8] Italy and Malta.[6] Moreover, interest is enhanced by the increased knowledge of the epidemiology and pathology of hepatic disorders, the latter of which is greatly aided by the basic investigations of Roholm and Iversen.[13] The classic conceptions such as catarrhal jaundice and alcoholic cirrhosis have been widely, if reluctantly, discarded in favor of the classification as toxipathic and trophopathic disorders, according to Himsworth and Glynn.[10] The former have toxic infectious causes, whereas the latter are due to some dietary deficiency. Thus the toxipathic disorders of the liver comprise all acute and many chronic forms of hepatitis, whereas the remaining forms of chronic hepatitis and cirrhosis must be regarded as trophopathic, and this applies presumably also to the alcoholic cirrhosis.

In Denmark, acute hepatitis has run a course parallel to that in the rest of the world. As shown in Table 1 an increased number of cases has been observed during the last 3 or 4 years, the disease being 7 to 8 times as frequent as usual.

Table 1.—Reported Case Incidence of Hepatitis in Denmark

	Entire country	Dept. B
1935	5,347	31
1936	2,761	21
1937	2,208	23
1938	2,257	25
1939	2,718	16
1940	3,079	19
1941	6,461	35
1942	10,819	36
1943	18,008	30
1944	15,977	46
1945	14,184	85

The increasing frequency has, as might be expected, reflected itself in most of the medical hospital departments over the country. An example of this can be seen in Table 1, where there is also given the total number of cases of acute and chronic hepatitis, treated in Medical Dept. B of Frederiksberg Hospital in the period 1935–1945. The explanation of the marked increase of acute hepatitis in a country like Denmark, however, still remains to be determined.

In Dept. B, however, it soon became evident that besides the increasing frequency of acute hepatitis, another problem presented itself—a problem of vital importance because of its seriousness and unusualness. Acute hepatitis tends to

run a benign course, terminating usually within a shorter or longer time in complete recovery. Now and then, however, a few cases are recorded which run either an acute lethal course or terminate in cirrhosis. Some of our cases developed differently. In 1944 and 1945 a considerable number of cases, instead of running the usual benign course, had a very protracted course. Many of these patients developed edema and ascites and death occurred in half of them. It was still more striking that this malignant hepatitis occurred almost exclusively in women over 45 years of age in contrast to acute infectious hepatitis, which ordinarily is most frequent in young men and women.

Malignant hepatitis is no isolated phenomenon. Björneboe and Bröchner-Mortensen[4] and Jersild[11] have published similar observations from the Municipal Hospital, Copenhagen and Bispebjerg Hospital, Copenhagen, but I am not aware of reports from countries other than Denmark.* Bergstrand,[2] however, in 1930, reported 150 similar cases, of which 97 occurred in Sweden in 1927. There are, however, essential differences between Bergstrand's cases and the disease as it appears in Copenhagen today. Among his 97 cases, 28% were male, and 36 of the cases occurred in persons under 40. On the other hand, the clinical course and pathology closely resemble that observed in Copenhagen during the 2 to 3 last years,

Because of the frequent incidence of malignant hepatitis, its serious and protracted course, and its high fatality rate, the following problems presented themselves: (1) Is the incidence of malignant hepatitis an outcome of the highly increased frequency of infectious hepatitis, *i. e.*, are cases of malignant hepatitis just severe cases of ordinary acute infectious hepatitis, or is this a new disease essentially different from acute hepatitis? (2) Is it possible at an early stage to establish a differential diagnosis between benign and malignant hepatitis? An answer to these questions is the primary object of the present studies.

Frequency and Sex Incidence in Malignant Hepatitis. As mentioned above the first cases of malignant hepatitis were observed in 1944. Consequently, I have collected and studied all cases of hepatitis and cirrhosis, treated in Dept B in the period of Jan. 1, 1944, to March 31, 1946. The relatively few cases of Laennec cirrhosis with an alcoholic etiology have been eliminated and the same applies to biliary and syphilitic cirrhosis (hepar lobatum) and "cirrhose cardiaque." This leaves 136 cases of which 27 were fatal. Postmortem examinations were performed in 24 cases. The incidence of the cases appears in Table 2.

Table 2.—Hepatitis in Dept. B. Jan. 1, 1944, to Mar. 31, 1946

	Men	Women	Total
Benign	41	41	82
Malignant:			
Surviving	0	27	27
Fatal	3	24	27
Total	44	92	136

The table shows that while the benign cases have had an equal sex distribution, the malignant cases have shown a marked female predominance and a fatality rate of 50%. Clinical criteria for the diagnosis of malignant hepatitis have been lethal exitus, development of portal stasis, or a clinical course of 4 months duration or more.

Age Distribution. The age distribution of the hepatitis patients appears in Tables 3 and 4.

The benign cases are put down in Table 3 and the malignant ones in Table 4. From these 2 tables it appears that benign hepatitis is most frequent in younger persons, and this is most marked in males where 38 of 41 men (93%) are under 45 years of age, while only 27 of 41 women (66%) are in the same age groups. Ordinarily the disease is still more frequent in chil-

* Since our receipt of this report, Baldwin Lucké and Tracy Mallory have reported (Am. J. Path. 22, 867, 1946) on 196 cases of fatal hepatitis in the U. S. Army of which 53% were of a fulminating type. —Editors.

dren under 15 years of age, but this is not manifest in our material data as Dept. B only admits a limited number of children.

TABLE 3.—AGE DISTRIBUTION IN BENIGN HEPATITIS

Years	Men	Women	Total
0–14	3	2	5
15–24	11	11	22
25–34	22	10	32
35–44	2	4	6
45–54	2	8	10
55–64	1	2	3
65–74	0	3	3
75–84	0	1	1
85 and over	0	0	0
Total	41	41	82

The age distribution in benign hepatitis is in striking contrast to the age distribution in malignant hepatitis. In the latter disease only 3 of 51 women (6%) are under 45 years of age, all of the 3 men being over 45 years of age. The numbers in brackets indicate fatal cases, averaging 50%. The fatality rate appears to increase with age.

TABLE 4.—AGE DISTRIBUTION IN MALIGNANT HEPATITIS

Years	Men	Women	Total
0–14	0	0	0
15–24	0	0	0
25–34	0	2 (0)	2 (0)
35–44	0	1 (0)	1 (0)
45–54	0	14 (7)	14 (7)
55–64	1 (1)	13 (5)	14 (6)
65–74	2 (2)	16 (9)	18 (11)
75–84	0	4 (3)	4 (3)
85 and over	0	1 (0)	1 (0)
Total	3 (3)	51 (24)	54 (27)

(Numbers in brackets are fatal cases)

LIVER FUNCTION TESTS. To obtain information about prognosis the results of various liver function tests performed on patients in both groups are being compared. In Dept. B few liver function tests are in use. On the other hand they have been repeatedly performed in all patients, because in our view it is preferable to apply few but familiar tests, the results of which can be reasonably well estimated, rather than to apply a greater number more or less at random. Beside the ordinary urinary tests, icterus index, Takata's reaction, Bauer's galactose test and determination of serum iron have been carried out repeatedly in all of these patients. The 3 blood tests mentioned have the advantage that they can be carried out on the same blood sample. The results are presented as follows: (1) immediately after admission, (2) the highest values observed during the clinical course and (3) the results before discharge or lethal exitus. It has not been possible to do this in all fatal cases as some of the patients died shortly after admission. In these cases a single group of tests only is given. In other patients the poor condition made the tests extremely difficult to obtain.

TABLE 5.—ICTERUS INDEX IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
41 male:				
On admission	38	93	3	7
During illness	38	93	3	7
On discharge	0		41	100
41 female:				
On admission	34	83	7	17
During illness	36	88	5	12
On discharge	2	5	39	95
B. Malignant cases:				
27 surviving:				
On admission	26	96	1	4
During illness	27	100	0	
On discharge	14	52	13	48
27 fatal:				
Before death	24	89	3	11

Icterus Index. In Table 5 the icterus index, according to the method of Meulengracht has been put down as positive or negative. Positive means an index of 15 or over. A high limit has intentionally been chosen to eliminate unequivocal results. The benign cases are subdivided into male and female cases while the malignant ones are subdivided into surviving and fatal cases. This arrangement is followed in the subsequent tables.

As appears from the table, about 90% of the benign cases had an icterus index of 15 or over on admission, or during the course of the disease. All patients, 2 women excepted, were discharged without jaundice. There was no difference between men and women. Those 10% or so of the patients who were not jaundiced

in hospital had been jaundiced at home prior to admission.

All surviving patients with malignant hepatitis were jaundiced on admission, or became jaundiced during the course of the illness. Half of them were still jaundiced on discharge, that is to say after a stay in hospital of several months duration. Of the 27 fatal cases, 3 were not jaundiced in hospital but had been on an earlier stage.

Accordingly, the icterus index provides no reliable informations with the exception that protracted jaundice is ominous, just as might be expected. A normal icterus index does not, on the other hand, guarantee against malignant hepatitis, as is evident from the 3 fatal non-jaundice cases.

TABLE 6.—TAKATA'S TEST IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
Male:				
36 on admission	3	8	33	92
14 during illness	1	7	13	93
20 on discharge	0		20	100
Female:				
33 on admission	4	12	29	88
17 during illness	1	6	16	94
24 on discharge	1	4	23	96
B. Malignant cases:				
Surviving:				
27 on admission	19	70	8	30
26 during illness	24	92	2	8
27 on discharge	18	67	9	33
Fatal:				
19 on admission	14	74	5	26
16 before death	14	87	2	13

Takata's Test. In Table 6 the results of Takata's test are recorded. Positive reaction means medium precipitation in at least 3 tubes, corresponding to the reaction generally indicated as ++. It will be observed that while Takata's test was negative in 90% of the benign cases on admission and, furthermore, became negative in all remaining benign cases, 1 case excepted, it was positive in from 70 to 74% of the malignant cases on admission. In the course of the disease 92% of the surviving patients with malignant hepatitis developed a positive Takata test, and it remained positive in 67% of these patients on discharge. In 16 patients Takata's test was carried out shortly before death; it was positive in 14 (87%). Takata's test indicates an abnormal albumin/globulin ratio in the plasma. In hepatitis this is due to a decreased albumin formation in the liver.

The data in Table 6 perhaps establishes the great differential diagnostic and prognostic value of Takata's test in hepatitis. As long as it remains negative a benign course is most likely, *ceteris paribus*. The reverse is still more pronounced; if the test becomes positive, and, especially, if it remains positive the case is probably a malignant one.

TABLE 7.—BAUER'S GALACTOSE TEST IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
Male:				
41 on admission	20	49	21	51
13 during illness	6	46	7	54
24 on discharge	12	50	12	50
Female:				
40 on admission	28	70	12	30
19 during illness	12	63	7	37
30 on admission	13	43	17	57
B. Malignant cases:				
Surviving:				
26 on admission	17	65	9	35
26 during illness	23	88	3	12
26 on discharge	19	73	7	27
Fatal:				
16 on admission	11	69	5	31
7 during illness	7	100	0	
9 before death	6	67	3	33

Bauer's Galactose Test. The results of the galactose tests are demonstrated in Table 7. The test has been regarded as positive when there has been a urinary excretion of 3 gm. of galactose. It is seen in the table that the test has been positive in half of the benign cases or so, and this percentage has remained practically unchanged during the disease even when all of the remaining clinical symptoms have disappeared.

In malignant cases a positive galactose test was somewhat more frequent, in almost 70% of the cases. During the further course of the disease it became positive in practically all cases, later again becoming negative in some cases, among

these even lethal ones. In many malignant cases there was a strikingly positive reaction with an excretion of more than 10 gm. of galactose. Apart from this inconstant finding the galactose test does not give any prognostic help worth mentioning. In cases where it runs a course parallel to Takata's test, it may eventually give some further support to the estimation of the character of the case. It is extraordinary to notice the frequent incidence of a positive galactose test in the malignant cases, the test, in my opinion, most usually being negative in the ordinary atrophic cirrhosis of Laennec.

Serum Iron. Determination of serum iron has been used for several years in Dept. B as a help in the differential diagnosis between hepatitis and obstructive jaundice. According to Bjerre and Christoffersen,[3] an elevation of the serum iron to 200 μg. per 100 ml. and over is observed in 70% of all cases of acute hepatitis, while normal or slightly lowered values are obtained in obstructive jaundice.

TABLE 8.—SERUM IRON IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
Male:				
40 on admission	7	18	33	82
31 during illness	16	52	15	48
34 on discharge	5	15	29	85
Female:				
38 on admission	8	21	30	79
27 during illness	11	41	16	59
35 on discharge	1	3	34	97
B. Malignant cases:				
Surviving:				
27 on admission	4	15	23	85
27 during illness	14	52	13	48
27 on discharge	1	4	26	96
Fatal:				
16 on admission	3	19	13	81
10 during illness	0		10	100
14 before death	0		14	100

In Table 8 are given the serum iron determinations in our cases. It appears that both in benign and malignant hepatitis a serum iron of more than 200 μg. per 100 ml. is found in half of the patients. In benign cases it later decreases, as a rule, somewhat more slowly than the icterus index, but in 10% of the patients it remains elevated above 200 μg. per ml. on discharge. In malignant cases the serum iron runs a similar course. It may be significant that normal values were obtained in all of the 14 patients examined immediately before death. It has to be admitted, however, that no great prognostic help is given by determination of serum iron in the malignant cases. At the very best one may get a slight indication, supporting or weakening a diagnosis based on other facts.

CLINICAL SYMPTOMS. *Ascites.* Development of ascites and edema must, as a matter of fact, be regarded as a very serious sign, provoked as it is partly by cirrhotic processes in the liver and partly by a lowered osmotic pressure in the plasma, due to deficient albumin formation in the liver.

TABLE 9.—ASCITES IN HEPATITIS

	Positive	Negative
A. Benign cases:		
82 male and female	0	82
B. Malignant cases:		
27 surviving:		
On admission	2	25
During illness	5	22
On discharge	2	25
Fatal:		
24 on admission	11	13
23 during illness	19	4
27 before death	20	7

In Table 9, the incidence of clinically demonstrable ascites in all of the patients is given. While ascites developed in none of the benign cases it was found on admission in 2 of the surviving malignant cases. In 3 of these cases considerable ascites developed during the illness, accompanied by pronounced edema of the legs. In all 3 patients, 2 younger and 1 older woman, however, ascites and edema disappeared little by little during some months as complete clinical recovery was observed and all function tests became normal. Thus a symptom as serious even as ascites must be estimated with reservation as to prognosis. That portal stasis still is extremely serious is sufficiently evident from the development in the fatal cases. On admission, ascites was found in 11 of

24 cases but at the time of death it was present in 20 of 27 patients.

Pain. In our few cases of malignant hepatitis a striking symptom was pain. Several of these patients suffered from repeated attacks of intense pain under the right costal margin. At first when the disease was new and unknown the diagnosis of gall stones was often made, and 2 of these patients had laparotomies performed. It is my impression that pain prevails chiefly in the early stages of the disease and that it is often accompanied by fever. In many malignant cases, however, pain never occurs. On the other hand, patients with infectious hepatitis not infrequently give a history of pain, as it is well known. In Table 10 is shown the incidence of pain in our material.

TABLE 10.—PAIN IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
41 male	12	29	29	71
41 female	7	17	34	83
B. Malignant cases:				
27 surviving	18	67	9	33
27 fatal	10	37	17	63

As will be seen, 23% of the benign cases give a history of pain. In the surviving malignant cases the corresponding number is 67% and in the fatal cases 37%. A numerical setting up of a symptom-like pain must always, however, be estimated with a certain reservation. As to pain its importance depends on its nature rather than on its frequency. In most of the benign cases the pain has manifested itself as a slight diffuse oppression in the abdomen. In malignant cases the pain most often occurs as attacks of intense ache, localized under the right curvature. Such attacks favor, if gall stones can be excluded, the diagnosis of malignant hepatitis. In this disease, however, pain is of no special serious prognostic importance, being more frequent in surviving than in fatal cases.

Blood. A symptom of frequent occurrence in hepatic cirrhosis is macrocytic anemia. As it might be possible to distinguish between benign and malignant hepatitis through differences in the blood pictures, red cell counts were done in 8 patients with benign hepatitis and in 13 surviving and 10 fatal cases of malignant hepatitis. All counts were performed on women. The mean results are to be found in Table 11.

TABLE 11.—MEAN BLOOD COUNTS

	Hemoglobin	R.B.C.	C.I.
A. Benign cases:			
8 female	88%	4.03	1.08
B. Malignant cases:			
13 surviving	76%	3.57	1.07
10 fatal	75%	3.41	1.10

It will be seen that the counts are somewhat lower in the malignant cases than in the benign ones. This was to be expected according to the age distribution of the disease. The difference, however, is so slight that it can hardly yield any diagnostic or prognostic help.

DURATION. The duration of the disease is shown in Table 12. The pre-icteric symptoms in hepatitis being rather vague and non-characteristic, the onset of the disease has been counted from the development of jaundice, this symptom being

TABLE 12.—DURATION OF SYMPTOMS (IN MONTHS)

	Less than 1	1	2	3	4	6	7	8	9	10	11	12 and over	Total
A. Benign cases:													
Male	15	18	5	3									41
Female	12	21	6	2									41
Total	27	39	11	5									82
B. Malignant cases:													
Fatal	1	2	4	5	3	3	3	0	1	1	1	0	3	27
Stationary	0	0	1	0	0	1	0	1	1	1	3	0	2	10
Improved or cured	0	0	0	1	6	0	1	4	1	0	1	0	3	17
Total	1	2	5	6	9	4	4	5	3	2	5	0	8	54

so conspicuous that it will hardly be overlooked long. The duration has in benign cases been counted until full clinical recovery, in malignant cases until death or discharge without regard to whether the discharge has taken place at full clinical recovery, considerable or only slight improvement or stationary condition during a longer period.

From the data it appears that the duration in most of the benign cases is less than 2 months and in the remaining ones 3 to 4 months. In a considerable number of cases, malignant hepatitis runs an acute course; thus no less than 12 of 54 patients died in less than 4 months. In most of the cases the duration was 4 to 9 months, only 8 lasting more than 1 year. These facts rather than the pathologic changes justify the term malignant hepatitis which must be preferred to the term chronic hepatitis even if many of the cases run a decidedly chronic course.

PATHOLOGIC ANATOMY. In 24 cases (3 male and 21 female) of a total of 27 fatal cases postmortems have been carried out. The pathologic findings have been strikingly uniform. It is remarkable how slightly the varying duration has influenced the pathologic changes. Macroscopically, the liver is extremely reduced in size, often being only half or two-thirds of its normal size. The form is unchanged in its broad features, the edges sharp. The consistency is tough, rather compact and yet flaccid. The surface shows an irregular finer or more coarse ruggedness and granulation, bigger and smaller roundish, smooth, bulging, yellowish or yellow-greenish areas, strongly contrasting with intervening darker, gray-red or gray-green, sunken, wrinkled areas, frequently of considerable extent. The cut surface exhibits a corresponding picture of slightly prominent, softer, dull, yellowish-green, yellowish islands of liver tissue, irregularly distributed in a cicatrized connective tissue which is sunken, smooth, more compact, grayish or red-grayish.

Microscopically, the prominent areas consist of islands of liver tissue, the cells of which show all stages of transition from apparently normal, newly formed cells, through turgid, granular and fatty degenerated cells to completely necrotic cells. Bile pigment lies free between or in the

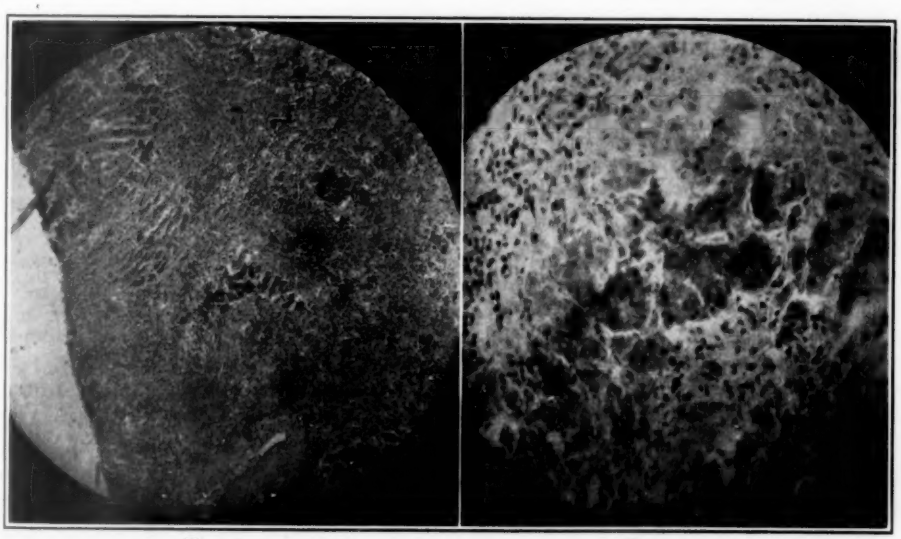

FIG. 1 FIG. 2

FIG. 1.—Section of liver showing liver cell islands surrounded by cicatrized connective tissue.
FIG. 2.—Same section as Figure 1, at higher magnification, showing degeneration of liver cells and lymphocyte infiltration.

cells, lobular delimitation is poor. In places where the tissue is best preserved necrosis and degeneration frequently seem to be most pronounced in the centers of the lobules. The outer zone, however, is often destroyed and lobules are dispersed in isolated bigger and smaller roundish groups of cells. The shrunken tissue between the islands of liver tissue consists of fibrous cicatrized tissue, containing varying numbers of capillaries with an increased number of leukocytes. Furthermore, there are numerous proliferated bile ducts with dark staining low cells, and here and there isolated liver cells or small groups and areas of these. The tissue is conspicuously infiltrated with lymphocytes, a few plasma cells, migrant cells and nuclear remnants, as well as scattered leukocytes. In the original portobiliary spaces the round cell infiltration assumes an almost follicular character.

As a whole, the picture conveys the impression of a continuous degenerative process, developing into necrosis with subsequent organization of the necrotic liver tissue and cicatrization, combined with endeavors of regeneration from the liver tissue and continued degeneration of the newly formed liver tissue.

The pathologic changes described here are characteristic of malignant hepatitis and distinctly different from those observed both in acute hepatitis and acute yellow atrophy. They are in close accordance with those reported by Bergstrand. Whether the changes in the initial stages of malignant hepatitis are characteristic of this disorder or correspond to those observed in acute hepatitis cannot be determined from this material, as no liver biopsies have been performed. Maybe the latter possibility is more likely, even if it is striking that in acute fatal cases changes were found, closely resembling those described above.

Likewise, the absence of liver biopsies prevents the information whether the pathologic changes decrease and disappear in patients with malignant hepatitis where clinical recovery is complete. This, of course, is a great lack, but we did not feel justified in exposing these patients with their small flaccid livers to the trauma of repeated liver biopsies.

ETIOLOGY. Infectious hepatitis is generally regarded as an infectious disease, caused by a filterable virus. Is malignant hepatitis just a variety of this disease, provoked by special factors, or is it a separate disease, perhaps not even an infectious one? It is difficult to answer the question at present. In its early stages the disease can hardly be distinguished from benign hepatitis but this does not prove that it is the same disease. Acute hepatitis and serum jaundice, for instance, are regarded as separate diseases because of their different time of incubation, in spite of their otherwise uniform course and uniform pathologic changes.*

Trying to find out whether in this material difference between the etiology in benign and malignant hepatitis can be traced, I have in Table 13 put down evidence that might be of etiologic importance.

TABLE 13.—ETIOLOGIC FACTORS

	Benign cases		Malignant cases	
	Male	Female	Surviving	Fatal
None	28	29	25	27
Contagion	11	3	1	0
Arsenic therapy	0	3	0	0
Syphilis	1	1	0	0
Pregnancy	0	2	1	0
Diabetes	1	3	0	0
Total	41	41	27	27

Table 13 shows that in 25 of 82 benign cases etiologically significant facts were found, 14 being cases with proved contact with patients suffering from hepatitis. In only 2 of 54 malignant cases could etiologic facts be traced. The numbers are small but even so the difference seems to be too big to be entirely casual; it rather

* Recent studies in the United States have given evidence that the viral etiologic agents of acute (infectious) hepatitis and homologous serum hepatitis are not identical and differ at least in their antigenic properties.—EDITORS.

suggests an etiology in malignant hepatitis different from the one in benign cases.

There is, however, another fact which still more corroborates this suggestion.

In Table 14 will be seen the total number of cases of acute infectious hepatitis in Denmark in the period 1935–45, subdivided for children, men and women. Furthermore the corresponding total number of deaths from acute and chronic hepatitis and cirrhosis is included. It is significant that while the increase of acute hepatitis since 1941 is most marked in children and men, the marked increased number of deaths in 1944 and 1945 only concerns the women, giving in 1945 a fatality rate of 11.5% of the total number of cases of hepatitis, while the male fatality rate is much lower than previously noted. This can, as far as I can see, only be explained by assuming that the greater part of the male deaths is due to the ordinary cirrhosis of Laennec, always a disease predominant in men, the incidence of which has remained unchanged in the last years, unaffected by the variations in the frequency of hepatitis. The great increase of female deaths must, however, be ascribed to malignant hepatitis, the conditions in the whole country thus corresponding exactly to those in Copenhagen.

If malignant hepatitis were nothing but a variety of acute infectious hepatitis, a distribution of the malignant cases might be expected that was in accordance with the distribution of the acute cases, but that is not so, neither in Dept. B nor in the entire country. As shown, the malignant form occurs practically only in women over 45 years of age, whereas the benign form is predominant in children and young men and women with a slight male predominance. This is in perfect accord with the conditions in Dept. B. Because of this fact and the etiologic differences suggested above, it seems thus far to be justifiable to maintain that acute infectious hepatitis and malignant hepatitis are 2 separate disorders. The former is of varying frequency, at times it is epidemic, and it is always predominant in young persons with an almost equal sex distribution. It is usually benign in its course, this also being the case in the recent epidemic outbreaks mentioned before. The latter has not been observed before 1944 and it occurs practically only in elderly women. It runs an extremely malignant course, having a fatality rate of 50%.

But even if malignant hepatitis is conceived as a separate entity, no explanation of its etiology has yet been given. It is not even known whether it is an infectious disease. Contagiousness has not been definitely proved and transmission experiments do not appear tempting with a disease of this nature. No other certain etiology has been substantiated. Gold and arsenic therapy and alcohol may decrease resistance against acute hepatitis[6] but these facts are absent in the material investigated here. The only features ap-

TABLE 14.—CASES OF INFECTIOUS HEPATITIS IN DENMARK 1935–45 AND DEATHS FROM HEPATITIS AND CIRRHOSIS IN THE SAME PERIOD

	Hepatitis			Deaths from hepatitis and cirrhosis				
					Men		Women	
	Children	Men	Women	Children	No.	%	No.	%
1935	3010	1221	1116	3	47	3.8	35	3.1
1936	1309	760	692	1	52	6.8	30	4.0
1937	975	607	626	2	54	8.9	18	2.9
1938	911	687	659	2	54	7.9	25	3.6
1939	1307	687	724	1	63	9.2	19	2.6
1940	1471	813	795	0	36	4.4	17	2.1
1941	2879	1854	1728	2	52	2.8	43	2.5
1942	4810	3310	2699	1	59	1.8	24	0.9
1943	7670	5605	4732	3	47	0.8	40	0.8
1944	6198	5249	4530	3	57	1.1	116	2.5
1945	4170	5376	4638	6	91	1.7	534	11.5

parently in common are the age and sex, 50 of 54 patients being climacteric or postclimacteric women. Only 1 woman is less than 35 years of age, the remaining 3 patients being elderly men. Obviously hormonal factors must be considered in the etiology but any particular information concerning this point cannot be obtained from the material presented here.

Repeated and complicated pregnancies might play a part in the later development of malignant hepatitis in these elderly women.

TABLE 15.—PREGNANCIES IN FEMALE CASES OF MALIGNANT HEPATITIS

Pregnancies	Surviving		Fatal	
0	15	68%	4	27%
1	4	32%	5	73%
2	1		3	
3	1		2	
4	1		1	
	22		15	
No information	5		9	
	27		24	

Table 15 gives the number of pregnancies in the female cases of malignant hepatitis as far as information has been available. The numbers are too small to be significant. They do seem to imply, however, that no more pregnancies have occurred among these women than among women in average. The reverse appears to be the case: the number of unmarried women being comparatively large. As to pregnancy no comparison can be made between benign and malignant hepatitis because of the different age distribution of the diseases.

All theories on the etiology in malignant hepatitis must therefore remain speculative. Demands on the liver caused by various vaccinations, so frequent in recent years, may play an etiologic rôle. It is difficult to understand, however, why this feature should be predominant in elderly women who would hardly be more frequently vaccinated than the remaining part of the population.

TREATMENT. The treatment in malignant hepatitis must be considered just as uncertain as the etiology. The treatment substantially is symptomatic, the chief principle being to do no damage. In Dept. B the patients have been given a balanced light diet with the addition of vitamins and symptomatic treatment as needed. Rest in bed has been considered the chief curative measure, the patients having been kept in bed until the disappearance of clinical symptoms or until the condition has remained stationary over a longer period.

Theoretically, an early treatment with methionine, cystine, choline or, eventually, estrin should be indicated. The treatment should begin at an early stage when the pathologic changes in the liver have only slightly developed, as it is difficult to imagine how any drug therapy should be able to influence pathologic changes of the character described above. Before it is possible to establish an early differential diagnosis between benign and malignant hepatitis it will, however, be extremely difficult if not impossible to estimate the therapeutic results, as all cases responding to treatment would, eventually, be conceived as benign cases.

Conclusion and Summary. One may conclude from the observations reported here that an extremely malignant form of hepatitis has been appearing in Denmark since 1944. It is predominant in women over 45 years of age and has a fatality rate of 50%. Most frequently its duration is from 4 to 9 months, but both a much more acute and a more protracted course may be observed. The clinical features are jaundice, frequent febrile attacks of pain and development of symptoms of portal stasis. As to prognosis, the result of Takata's test is important, whereas the remaining liver function tests applied are of secondary value only. The lesions are characterized by destruction of the liver tissue, and in the more chronic cases development of a cicatrized connective tissue. Therefore, the etiology is obscure. Both etiologically and clinically the disease differs in essential points from acute infectious hepatitis. The treatment has until now been entirely symptomatic.

Not wishing to delay this important article by communicating with the author in Denmark, we venture to suggest a different interpretation from that given above; namely, that the increased incidence in both sexes may be due to the spread of the virus of epidemic hepatitis in sufficiently benign form to lower the mortality *rate* in both sexes, though, for reasons still unknown, the mortality rate in 1944 and 1945 is much higher in women than in men.—EDITORS.

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DIAGNOSIS OF ACUTE RESPIRATORY TRACT INFECTIONS*

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During the past several years we have had an opportunity to study patients with acute respiratory tract infections, particularly those with primary atypical pneumonia, and the results of certain investigations have been published.[1,5] During the course of the study patients were admitted to this hospital who were thought to have primary atypical pneumonia. Following careful examination some of the patients seemed clearly to have respiratory infections of another sort, and in others revision of the initial diagnosis was made necessary by subsequent laboratory findings. The results of studies on these patients serve to call attention to the difficulties of accurate clinical diagnosis of acute respiratory infections. It is the purpose of this communication to emphasize these difficulties, to assess the extent to which laboratory studies may serve to establish accurate diagnoses in such conditions, and to present evidence indicating that more than one infectious agent may be operative in some instances of acute respiratory infection. For the purposes of this study the attitude was adopted that all final diagnoses were to depend upon positive laboratory evidence. In those instances in which only negative laboratory data were obtained, a specific final diagnosis was not assigned.

Patients and Methods. *Patients.* The 26 patients included in this report are made up of 2 small groups, each admitted to the Hospital of The Rockefeller Institute during mild influenza epidemics in the New York area, 1 in the winter of 1943–44 (influenza A) and the other in the winter of 1945–46 (influenza B). In each group patients are included who were admitted between the first and last cases showing evidence of influenza virus infection. The patients are few in number, all but 1 were in military service, and they were young, previously healthy adults. These facts, which might be regarded as objectionable were an attempt made to draw general inferences from the groups, obviously do not weigh against consideration of each patient as an individual diagnostic problem.

Procedure. On admission, after a history was obtained, each patient was examined. Roentgen rays of the chest were taken, swabbings of the nasopharynx were obtained, and blood was drawn for culture as well as for hematologic and serologic studies. Sputum was collected when available. Nasopharyngeal washings were collected from selected patients. Some of these procedures were repeated at weekly or more frequent intervals.

Bacteriologic Procedures. Swabbings of the nose and throat were streaked on rabbit blood agar plates. Sputum was similarly cultured. Either a small amount of sputum or the throat swab was also cultured in a selective medium to facilitate the isolation of certain non-hemolytic streptococci.[5] Sputum, or a portion of the throat washings, was inoculated intraperitoneally in a mouse. A stained smear of the sputum was made, and if it showed organisms resembling pneumococcus, an attempt was made to identify this organism by the direct "quellung" technique.

* The Bureau of Medicine and Surgery does not necessarily undertake to endorse the views or opinions which are expressed in this paper.

In the identification of organisms recovered by these methods, various procedures were employed. Certain common nose and throat organisms were identified by their colony characteristics and appearance on stained smears; these included the staphylococci, organisms of the Neisseria group, *Hemophilus hemolyticus* and diphtheroids. Organisms resembling beta-hemolytic streptococcus, pneumococcus or *Hemophilus influenzæ* were further identified. Those suspected of being beta-hemolytic streptococci were subcultured, extracted, and the extracts set up against diagnostic serum for each Lancefield group; organisms belonging to Group A were typed by the Lancefield precipitin technique. Strains of pneumococcus were identified by the "quellung" method, employing sera for Types I through XLIII. Organisms resembling *H. influenzæ* were routinely tested by the "quellung" method using typing sera A through F. Non-hemolytic streptococci recovered in the selective medium were grown on 5% sucrose agar, to distinguish *Str. salivarius* from the organism known as streptococcus MG,[5] and further identified by the "quellung" technique with antistreptococcus MG serum.

Influenza Virus Identification. Strains of influenza virus were recovered by the inoculation of throat washings into the amniotic sac of the chick embryo. The presence of virus in embryonic fluids was recognized by chicken erythrocyte agglutination, and the virus was identified by the inhibition of this effect with specific antisera against influenza A or B virus.

Serologic Procedures. Standard methods were employed in testing the sera for pneumococcus agglutinins, streptococcus MG agglutinins,[5] cold hemagglutinins,[4] influenza virus antibodies,[2] and antistreptolysin O.[6] The antistreptolysin O tests were done through the courtesy of Dr. Sidney Rothbard of the Hospital of The Rockefeller Institute.

LABORATORY STUDIES, RESULTS AND INTERPRETATION. The patients included in this study are listed in Table 1 in the order of their admission. Their initial diagnoses, laboratory findings, and final diagnoses are shown. Since one purpose was to relate laboratory data to the clinical picture, the laboratory findings and the serologic tests employed, as well as the criteria for their evaluation will be discussed. The relation of the initial diagnosis to the final diagnosis will be considered later.

1. *Pneumococcus.* As shown in Table 1, pneumococcus was recovered from 12 patients. Types 4, 7 (Case 14), 19 and 28 were typed directly in the sputum. Type 7 (Case 25) grew in pure culture from nasal swabs. Type 43 was obtained from nose and throat cultures. Types 3, 6, 8, 13, 15 and 34 were recovered only after mouse inoculation, and could not be identified in nose, throat or sputum cultures.

Acute and convalescent sera from each patient from whom pneumococcus was recovered were tested for the presence of agglutinins against the homologous type. The results are to be seen in Table 1. Agglutinins were present in none of the acute sera in a dilution of 1:10. Agglutinins in low titer developed in the convalescent sera of both patients with Type 7 (Cases 14 and 25) and in the serum of the patient with Type 8 (Case 26). The reason for the failure to identify pneumococcus directly in the sputum of Case 26 and in Case 25 was probably attributable to previous treatment, in 1 case with sulfadiazine, in the other with penicillin. Case 16 failed to develop demonstrable agglutinins against Type 4, but mouse protective antibody was present in serum obtained on the 8th day and attained high titer later. The course and serologic findings warrant a diagnosis of pneumococcal pneumonia in Cases 14, 16, 25 and 26.

No positive evidence was obtained regarding the rôle of pneumococci in the patients with bronchitis but without pneumonia. The direct identification of Type 28, in the sputum of Case 23, is of doubtful significance; this patient developed significant titers of both cold hemagglutinins and streptococcus MG agglutinins.

2. *Beta-hemolytic Streptococcus.* Beta-hemolytic streptococci were recovered from the nose, throat or sputum of 8 patients. One organism (Case 20) belonged to Group B and another (Case 12) to Group G; the remainder were Group A.

In 4 instances (Cases 1, 17, 19, 21) the streptococci were present in large numbers; in 2 (Cases 23 and 24) only a few colonies were seen. The streptococci from Cases 1, 19 and 23 were not typable, Cases 21 and 24 both had Type 3, and Case 17 Type 17.

Acute and convalescent sera from each patient with a Group A streptococcus were tested for antistreptolysin O content. In this test the degree to which serum inhibits hemolysis of erythrocytes by streptolysin O, derived from Group A beta-hemolytic streptococcus, is measured. The antistreptolysin titers of sera from these patients are recorded in Table 1. Evidence of infection by Group A organisms rests not upon the titer of a single serum, but upon the *increase* in antistreptolysin titer during convalescence as compared to that present in the acute phase of illness.

None of these patients was thought to have more than the moderate pharyngitis common to many acute respiratory infections and only 3 (Cases 19, 23 and 24) complained of sore throat. Two of these (Cases 19 and 24) were among the 3 patients (Cases 19, 21 and 24) who showed a significant rise in antistreptolysin titer. Of the other 3 patients, 2 (Cases 17 and 23) showed normal antistreptolysin levels without a significant rise in convalescence, the other (Case 1) showed a persistently high level, suggesting a carrier state following infection, of which, however, there was no history.

The benign rôle of beta-hemolytic streptococci in the patients with influenza is of interest since the combination might be expected to produce serious disease. That this may occur is evidenced by 1 patient, not included in this study, with a history and serologic evidence of a very recent influenza B virus infection who was admitted with a scarlatiniform rash and pneumonia, complicated by a massive pleural effusion, from whom beta-hemolytic streptococcus, Group A, Type 3, was recovered. Even with sulfadiazine and penicillin therapy, to both of which drugs this organism was susceptible, this patient was critically ill for 7 days.

3. *Influenza Viruses.* No attempt was made to recover influenza virus from all patients. It is of interest that in 1945 the initial diagnosis of influenza in Case 17 was confirmed within 48 hours, by the recovery of influenza B virus from the throat washing. In every case, acute and convalescent sera were tested for antibodies against both influenza A and B viruses.

Influenza viruses possess the property of agglutinating erythrocytes of certain species. Without respect to recent infection many human sera possess the capacity, in greater or lesser degree, of inhibiting the phenomenon of hemagglutination. However, the agglutination-inhibition titer of serum from a patient convalescing from an influenza virus infection, when compared with the titer of serum obtained during the acute phase, usually shows a considerable increase directed specifically against the influenza virus (A or B) by which the individual was infected. If the agglutination-inhibition titer of a convalescent serum with respect to one or the other of the influenza viruses is 4 or more times greater than the acute phase serum titer, a diagnosis of infection by that influenza virus may be made with assurance.

In Table 1 the serum titers against both influenza A and influenza B viruses are expressed for each patient by a value representing the arithmetical increase of the convalescent titer as compared with the acute phase titer. For 2 patients (Cases 21 and 23) the actual titers are given since, although a rise could not be shown, they were each admitted after more than 1 week from onset with titers high enough to warrant a presumptive diagnosis of influenza.

It may be seen that during periods when infection by influenza viruses was prevalent many, but not all, of the cases of acute respiratory disease showed evidence of influenza virus infection. Of the 26 patients with respiratory disease admitted

Patient		Admission clinical impression	Duration of illness on admission (Days)	Laboratory findings				Serological findings						Final diagnosis	Case number
Case number	Age			Admission W.B.C. (Thousands)	Pneumococcus (Type)	Beta-hemolytic streptococcus (Group + type)	Non-hemolytic streptococcus (MG)	Pneumococcus agglutinins	Antistreptolysin O	Influenza virus agglutination inhibition A	Influenza virus agglutination inhibition B	Streptococcus MG agglutinins	Cold hemagglutinins		
1943 – 1944															
1	18	PAP	8	9.5	0	A(?)	+	–	200/200	8	2	10	20	PAP Influenza A	1
2	36	PAP	3	7.5	0	0	0	–	–	>8	1	10	0	Influenza A	2
3	24	Bronchitis	3	3.9	13	0	0	0	–	4	1	0	40/40	Influenza A	3
4	22	URI	6	7.5	0	0	0	–	–	16	1 2	0	0	Influenza A possible PAP	4
5	35	PAP	3	3.5	0	0	0	–	–	8	1	40	0	PAP Influenza A	5
6	35	PAP	4	6.1	0	0	0	–	–	1	1	20	20	PAP	6
7	21	PAP	4	6.8	34	0	0	0	–	1	1	20	40	Bronchitis resembling PAP	7
8	22	URI	4	7.7	0	0	0	–	–	8	1	0	0	Influenza A	8
9	25	Influenza	1	6.0	3	0	+	0	–	4	1	0	0	Influenza A	9
10	31	Influenza	5	5.2	0	0	0	–	–	32	1	0	0	Influenza A	10
11	38	Influenza	1	5.1	0	0	0	–	–	8	1	0	10	Influenza A	11
12	22	URI	2	9.2	6	G	0	0	–	4	1	10	0	Influenza A	12
1945 – 1946															
13	19	Influenza	1	7.3	0	0	0	–	–	1.3	64	0	0	Influenza B	13
14	22	PAP	5	6.9	7 direct	0	0	10	–	1	1	0	0	Pneumococcal pneumonia type 7	14
15	43	PAP	17	14.7	0	0	+	–	–	1	1	0	80/20	PAP	15
16	21	PAP	8?	9.0	4 direct	0	+	§0	–	1	29	10	0	Pneumococcal pneumonia type 4 Influenza B	16
17	18	Influenza	1	7.9	0	A,17	+	–	100/75	0.8	8	0	0	Influenza B possible PAP	17
18	20	Influenza	1	14.9	19 direct	0	+	0	–	1	1	0	0	U.R.I.	18
19	18	Influenza	1	7.3	0	A (?)	+	–	75/250	1	15	10/10	0	Influenza B B.H.S. infection	19
20	30	PAP	6	5.9	0	B	0	–	–	1	1.3	160	160/320	PAP	20
21	24	PAP	14	7.8	0	A,3	0	–	75/150	160/80	2560/1280	20/20	0	PAP Influenza B B.H.S. infection	21
22	18	PAP	8	8.0	43	0	+	0	–	1	1	0	0	Possible PAP	22
23	19	PAP	8	9.8	28 direct	A (?)	0	0	75/100	1	2560/1920	40	20/80	PAP Influenza B	23
24	17	Influenza	1	7.7	15	A,3	0	0	300/500	3	0.8	20	40	Influenza A B.H.S. infection	24
25	18	PAP	5	17.6	7	0	0	10	–	1	1	0	0	Pneumococcal pneumonia type 7	25
26	18	PAP	3	3.8	8	0	0	10	–	1.5	1	0	0	Pneumococcal pneumonia type 8	26

TABLE 1.—P.A.P. = Primary Atypical Pneumonia. U.R.I. = Upper Respiratory Tract Infection. B.H.S. = Beta-hemolytic Streptococcus. * = Single figures in these columns represent the highest serum titer observed in convalescence, where the acute phase serum titer was <5 (pneumococcus agglutinins) or <10 (streptococcus MG agglutinins and cold hemagglutinins). ‡ = Where figures appear as fractions the numerator represents the serum titer on admission, the denominator represents the serum titer in convalescence. ** = Influenza virus agglutination inhibition titers are represented by a figure denoting the arithmetic increase of convalescent serum titer over acute-phase serum titer. § = This patient developed significant mouse-protective antibody against his pneumococcus.

during 2 epidemic periods, 17 showed evidence of infection with an influenza virus. One patient (Case 24) gave evidence of influenza A virus infection at a time when influenza B was epidemic. The antibody titer of this patient's convalescent serum was only 3 times greater than that of his acute phase serum. However, this increase was repeatedly demonstrable, was apparent also in a chick embryo protection test, and is very probably significant. Attempts to recover influenza virus from this patient were unsuccessful. This patient illustrates the fact that cases of infection by one of the influenza viruses when the other virus is epidemic, though uncommon, do occur.

Cases 4 and 17 showed serologic evidence of influenza virus infection, and influenza B virus was recovered from Case 17. Case 4 presented physical and Roentgen ray signs of pulmonary involvement on admission. In Case 17 a hazy but definite right lower lobe shadow, not present on admission, was seen in a Roentgen ray on the 4th day; it disappeared during convalescence, and was unaccompanied by physical signs. In Case 4, no significant bacteria were recovered. Case 17 showed in throat culture beta-hemolytic streptococcus, Group A, Type 17, but antistreptolysin O tests gave no evidence that this organism had caused infection. Both cases, therefore, represent examples of influenza virus infection associated with pneumonia of undetermined etiology, and again raise the question of whether the influenza viruses, which are capable of causing pneumonia in other susceptible species, are also capable of effecting a similar pathologic pattern in man.

4. *H. Influenzæ Group.* Organisms resembling *H. influenzæ* were recovered from 6 patients (Cases 5, 6, 16, 17, 22 and 23); none was typable and except in 1 patient (Case 22) in which they were the predominant organism in the sputum, they were present only in small numbers.

5. *Non-hemolytic Streptococcus (MG).* Eight patients (Cases 1, 9, 15, 16, 17, 18, 19 and 22) showed streptococcus MG in cultures of sputum or throat. Of these, only 2 (Cases 1 and 16) developed agglutinins against this organism. The incidence of streptococcus MG in this study is similar to that previously found in various types of respiratory disease.[5] The mere isolation of this organism from the sputum or throat appears not to be of diagnostic import.

6. *Cold Hemagglutinins and Streptococcus MG Agglutinins.* The development in the serum of a patient with pneumonia of cold hemagglutinins[4] or of agglutinins against a non-hemolytic streptococcus designated as streptococcus MG,[5] is of confirmatory value in making a diagnosis of primary atypical pneumonia.

The available published data on both these tests have been summarized in a recent discussion by Horsfall.[3] Streptococcus MG agglutination tests have been reported on more than 1000 persons who can be divided into 3 groups: those with a clinical diagnosis of primary atypical pneumonia, those with clinical diagnoses of other acute infections, and normal persons. Streptococcus MG agglutinin titers of 1:20 or more were found in the sera of approximately half (48.9%) of the patients with primary atypical pneumonia, whereas in each of the other 2 groups comparable titers were found in only 5%. When acute phase and convalescent serum titers were compared, significant *increases* in titer (fourfold or more) were limited with but rare exception to primary atypical pneumonia. The published data on the occurrence of cold hemagglutinins in similar groups provide information on more than 2000 persons upon whose sera the test was carried out in a standard manner. Titers of cold hemagglutinins of 1:40 or more were found in the sera of 54.4% of the primary atypical pneumonia group, in 2% of the group with "other infections" and in none of the "normals."

The significance of the occurrence of either of these agglutinins in normal persons or in patients with acute infections other than primary atypical pneumonia cannot as yet be determined. Where the

clinical diagnosis of an acute respiratory disease associated with pneumonia is doubtful, a convalescent *rise* in the titer of either agglutinin to a level of 1:20 or more suggests that the disease should be classified as primary atypical pneumonia. It is of interest that such a rise in either or both agglutinins developed in 9 patients in the present series, of whom 8 had physical or Roentgen ray signs of lung involvement, and in only 1 of 6 patients without positive lung findings. The results of streptococcus MG agglutination and cold hemagglutination tests are recorded in Table 1.

Patients with Titers of Streptococcus MG Agglutinins or Cold Hemagglutinins of 1:20 or More. Titers of either agglutinin attained levels of 1:20 or more in the convalescent sera of 8 patients (Cases 1, 5, 6, 7, 15, 20, 23 and 24). In 2 patients agglutinin titers were in this range on admission and remained constant until discharge; Case 21, admitted on the 14th day following onset showed an agglutination titer against streptococcus MG of 1:20, and Case 3 maintained a constant cold hemagglutination titer of 1:40.

Of this group, 3 patients (6, 15 and 20) appeared clinically and on the basis of these serologic tests, to have primary atypical pneumonia; in none of them were the bacteriologic or other serologic findings of positive diagnostic significance.

The presence of significant titers of either of these agglutinins is somewhat more difficult to interpret in Cases 1, 5 and 23. In each of these cases the illness and Roentgen ray findings were consistent with atypical pneumonia. In addition, however, all presented serologic evidence of infection by one of the influenza viruses, and from Cases 1 and 23 a Group A beta-hemolytic streptococcus was recovered. In the last 2 patients there was no serologic evidence that hemolytic streptococcus was implicated in the disease. In Case 1 the cold hemagglutinin titer of 1:20 favors a diagnosis of primary atypical pneumonia; a titer of this height is rare in influenza, but occurs frequently in primary atypical pneumonia. The simultaneous rise in streptococcus MG agglutinins supports this interpretation, since the titers of this agglutinin have not been observed to increase as a result of influenza. In Cases 5 and 23 diagnosis is less difficult, since both developed streptococcus MG agglutinin titers of 1:40, and Case 23 also acquired a cold hemagglutinin titer of 1:80. The possibility that Type 28 pneumococcus played a part in the latter patient's disease has already been considered to be unlikely. In these 3 patients the evidence suggests concurrent infection by one of the influenza viruses and the agent or agents responsible for primary atypical pneumonia. It is probable that Case 21 also belongs in this group. This patient was admitted late in the course of illness and maintained a constant titer of agglutinins against streptococcus MG of 1:20. He also showed evidence of influenza B virus infection, and carried Group A hemolytic streptococcus, with serologic evidence of infection by this organism.

Case 7 had an illness clinically resembling primary atypical pneumonia with physical signs of lung involvement but without Roentgen ray evidence of pneumonia. During convalescence this patient developed a titer of 1:20 against streptococcus MG and a cold hemagglutinin titer of 1:40. Case 24 developed both streptococcus MG agglutinins (1:20) and cold hemagglutinins (1:40) without physical or Roentgen ray evidence of pneumonia; the relationship of these agglutinins to the patient's disease, in which there was serologic evidence of infection by both influenza A virus and Group A hemolytic streptococcus, is not apparent. Case 3 had an influenza A virus infection, with acute bronchitis without Roentgen ray evidence of pneumonia. Serum obtained on the 3rd day of illness possessed a cold hemagglutinin titer of 1:40, which persisted during his hospital stay. To which aspect of his illness this should be ascribed is impossible to decide.

Patients With Titers of Streptococcus MG Agglutinins or Cold Hemagglutinins of Less

than 1:20. The sera of 5 patients (Cases 2, 11, 12, 16, 19) showed either streptococcus MG agglutinins, or cold hemagglutinins in a titer of less than 1:20, but in the first 4 instances this represented an increase in titer. It may be of significance that in each of these 4 cases there was physical evidence of lung involvement, although in Case 16, the only one with Roentgen ray evidence of pneumonia, Type 4 pneumococcus appeared to be the etiologic agent. In addition each of these 4 cases gave serologic evidence of influenza. The remaining patient (Case 19) had neither physical nor Roentgen ray signs of pneumonia, but showed serologic evidence of both influenza and Group A beta-hemolytic streptococcus infection, with a streptococcus MG agglutinin titer of 1:10 which remained unchanged during his hospital stay.

In these cases no reliable interpretation of either streptococcus MG agglutinin or cold hemagglutinin titers of less than 1:20 appears to be possible.

7. *Patients Without Positive Serologic Response.* Cases 18 and 22 failed to develop demonstrable antibodies against the pneumococci isolated from them, or either of the influenza viruses, and did not develop either cold or streptococcus MG agglutinins.

Clinical Impressions on Admission and Their Relation to Final Diagnosis. From the serologic data it appears that in these patients with acute infections of the respiratory tract, a number of different infectious agents (including the agent or agents of primary atypical pneumonia) were responsible for the illnesses observed, and furthermore, that in certain instances 2 or more infectious agents were implicated together. The question which is of present interest is whether the laboratory findings, the clinical impression in each case, and the final classification of the patient's disease may be integrated. An attempt to establish such correlations discloses some of the difficulties and errors often encountered but more often overlooked in the diagnosis of these diseases.

It was the practice in each case to record a clinical impression before the results of Roentgen ray or laboratory examinations were known. In Table 2 the presenting symptoms and relevant physical findings of each of the patients under consideration are shown, with the clinical impression and final diagnosis.

1. *Beta - hemolytic Streptococcal Infections.* In none of the initial clinical impressions was the possibility considered that these patients might have beta-hemolytic streptococcus infections, yet from 6 cases a Group A organism was isolated, and in 3 serologic evidence of infection was also obtained. In none of these patients did the signs or symptoms suggest infection by this organism.

2. *Influenza.* A diagnosis of influenza was made on admission in 8 patients (Cases 9, 10, 11, 13, 17, 18, 19 and 24) and in 7 it remained the final diagnosis. Case 18, the exception, is discussed below. It is significant, in view of the number of patients shown to have an influenza virus infection which was not diagnosed clinically, that all of these patients were admitted to the hospital on the 1st day of their illness, with the exception of Case 10, a physician who treated himself at home. All of these patients were acutely ill and were hospitalized promptly. The fact that the initial diagnoses in these cases were correct may be attributed in part to accurate appraisal of the clinical manifestations of acute infection with relatively marked constitutional symptoms, observed soon after the abrupt onset, but chiefly to the fact that the patients presented symptoms that were compatible with a diagnosis of influenza at a time when influenza (A or B) was *known* to be present in epidemic form.

In the 7 patients with influenza whose disease was diagnosed correctly on admission, the symptoms were varied. In all the onset of the illness was sudden, and in only 2 was it preceded by respiratory symptoms of any sort. All of the patients had fever. All but 1 of the patients had a cough, but in only 4 (Cases 11, 17, 19

Patient: Case number	Age	Admission clinical impression	Duration of illness on admission (Days)	Symptoms (in order of frequency): Malaise and fever	Cough	Sudden onset	Headache	Generalized aching	Sputum	Rigor	Previous URI	Sore throat	Epistaxis	Nausea	Vomiting	Abnormal lung findings *(location): Physical	X-ray	Final diagnosis	Case number
1943 - 1944																			
1	18	P.A.P.	8													LL	LL	P.A.P. Influenza A	1
2	36	P.A.P.	3													RL LL	0	Influenza A	2
3	24	Bronchitis	3													LL	0	Influenza A	3
4	22	U.R.I.	6													RL	RL	Influenza A possible P.A.P.	4
5	35	P.A.P.	3													RL	RL	P.A.P. Influenza A	5
6	35	P.A.P.	4													LL	LL	P.A.P.	6
7	21	P.A.P.	4													LL	0	Bronchitis resembling P.A.P.	7
8	22	U.R.I.	4													0	0	Influenza A	8
9	25	Influenza	1													0	0	Influenza A	9
10	31	Influenza	5													0	0	Influenza A	10
11	38	Influenza	1													RL LL	0	Influenza A	11
12	22	U.R.I.	2													RL	0	Influenza A	12
1945 - 1946																			
13	19	Influenza	1													0	0	Influenza B	13
14	22	P.A.P.	5													0	RL	Pneumococcal pneumonia type 7	14
15	43	P.A.P.	17													RL	RL	P.A.P.	15
16	21	P.A.P.	8?													RU	RU	Pneumococcal pneumonia type 4 Influenza B	16
17	18	Influenza	1													0	RL	Influenza B possible P.A.P.	17
18	20	Influenza	1													0	0	U.R.I.	18
19	18	Influenza	1													0	0	Influenza B B.H.S. infection	19
20	30	P.A.P.	6													RL	RL	P.A.P.	20
21	24	P.A.P.	14													RL	RL	P.A.P. Influenza B B.H.S. infection	21
22	18	P.A.P.	8													0	RL	Possible P.A.P.	22
23	19	P.A.P.	8													RL	LL	P.A.P. Influenza B	23
24	17	Influenza	1													0	0	Influenza A B.H.S. infection	24
25	18	P.A.P.	5													RL	RL	Pneumococcal pneumonia type 7	25
26	18	P.A.P.	3													0	LL	Pneumococcal pneumonia type 8	26

TABLE 2.—P.A.P. = Primary Atypical Pneumonia. U.R.I. = Upper Respiratory Tract Infection. B.H.S. = Beta-hemolytic Streptococcus. RL, LL = Right lower lobe, left lower lobe, etc.; refers to area of lung in which any abnormal findings from persistent râles to signs of consolidation were localized.

and 24) was it productive. In 4 of the patients the onset of disease was accompanied by a rigor, and in 1, such chills recurred for some days. Six of the patients complained of generalized aching, the other did not. Among other symptoms may be mentioned headache in 5, sore throat in 4, nausea and vomiting in 1, and epistaxis in another. Positive physical findings were few. All of the patients looked acutely ill, and all had a mild to moderate degree of nasopharyngitis. Only one showed flushing of the face and upper thorax, so often described as "typical." One patient had a few râles at 1 lung base (Case 11) and another (Case 17) developed a right lower lobe shadow late in his disease. All the leukocyte counts were normal. In 3 patients the sedimentation rate was normal (less than 10 mm.) on admission, and remained so; the other 4 patients (Cases 10, 11, 19 and 24) had elevated rates around 30 mm. which persisted to the time of discharge.

Case 24, in whom positive clinical findings were limited to a moderate nasopharyngitis, presented a puzzling array of laboratory findings, with initial neutropenia and the recovery of Group A beta-hemolytic streptococcus, Type 3, from his throat, and pneumococcus, Type 15, from sputum after mouse inoculation. In this case the convalescent titers of influenza A virus antibody and antistreptolysin are interpretable; the development of significant titers of both streptococcus MG agglutinins and cold hemagglutinins, is not.

Case 18, diagnosed as influenza, had an acute upper respiratory tract infection, with fever lasting only 24 hours. Type 19 pneumococcus was found on direct typing of his sputum, and his white blood cell count was elevated. Serologic tests failed to confirm the clinical diagnosis, and did not provide any positive evidence that the pneumococcus was implicated in his disease.

3. "*Upper Respiratory Tract Infection.*" Three cases called upper respiratory tract infection on admission (Cases 4, 8 and 12) were later shown to have had influenza A virus infections. These individuals presented no very different symptoms from the previous group, but this non-committal diagnostic impression may have been determined by the fact that they were first seen on the 6th, 4th and 2nd days, respectively, of their illnesses, when the symptoms and findings at onset were a matter of history rather than observation.

The admission white blood counts in these cases ranged from 7.2 to 9.2 thousand. On admission no significant organisms were identified with the exception of Type 6 pneumococcus in Case 12, which was recovered only on mouse inoculation of sputum.

The admission impressions were modified in Cases 8 and 12 only by the serologic evidence of influenza A infection. In Case 4 the demonstration of a shadow in the right lower lobe on admission Roentgen ray before physical signs were evident, changed the clinical impression to primary atypical pneumonia. Later serologic tests showed that the patient had had influenza A infection, but gave no confirmatory evidence regarding the cause of his pneumonia, which remains undetermined, although it may belong in the primary atypical pneumonia group.

4. *Acute Bronchitis.* In a single patient (Case 3) an admission diagnosis of bronchitis was made. Although this patient had signs of bronchitis his illness was not distinguishable from many others in the group, and from the laboratory evidence only a diagnosis of influenza A could be made. The occurrence of a constant moderately high level of cold hemagglutinins in his serum is unexplained.

5. *Primary Atypical Pneumonia.* The clinical impression of primary atypical pneumonia was recorded on admission for 14 patients. In contrast to the group initially diagnosed as influenza, only 2 of this group of patients were seen as early as the 3rd day of illness, and the average duration of illness before admission was 6.8 days. Serologic evidence confirmed the admission impression in 8 cases; in the 6 remaining cases, a different diagnosis

was established in 5, and in 1 a positive diagnosis was not established. In several instances serologic results necessitated additional diagnoses, principally of influenza A or B.

Cases in Which the Clinical Impression of Primary Atypical Pneumonia Was Confirmed Serologically. In 7 patients (Cases 1, 5, 6, 15, 20, 21 and 23) both Roentgen ray and serologic findings confirmed the admission impression of primary atypical pneumonia, and in an additional patient (Case 7) the clinical and serologic findings warrant the inclusion of the patient in this group, although Roentgen ray evidence of pneumonia was lacking. In this group of patients symptoms were variable and there was no significant clinical difference between those who had concurrent influenza and those who did not. Except for the results of chest examinations the physical findings were not very striking. These patients were neither so acutely ill nor so prostrated as patients with uncomplicated influenza and Case 5 was the only patient whose course suggested that concurrent influenza and primary atypical pneumonia may be more severe than either disease alone. The average white blood count on admission was 9.6 thousand. There was 1 example of leukopenia (Case 5, with concurrent influenza) and 1 of leukocytosis (Case 15). The sedimentation rate was elevated in all patients except Case 4. Admission bacteriologic findings did not lead to any alterations of the original clinical impressions, although Group A beta-hemolytic streptococci were recovered from 3 of the patients (Cases 1, 21 and 23). There was no clinical evidence suggesting infection by these organisms. From Case 23 Type 28 pneumococcus was identified directly in sputum, but its significance was doubtful.

Serologic results confirmed the diagnosis of primary atypical pneumonia in all of these patients, and led to additional diagnoses of influenza virus infection in Cases 1, 5, 21 and 23. Cases 1 and 5 gave evidence of concurrent influenza A; both Cases 21 and 23 showed presumptive evidence of influenza B, with very high antibody levels on admission (the 14th and 9th days, respectively of their illnesses). The history of Case 21 suggested 2 distinguishable but merging episodes of infection of which the first probably represented influenza B, and the second, primary atypical pneumonia; in the other patients no such biphasic pattern could be made out. In Case 21, serologic findings necessitated a third diagnosis of concurrent beta-hemolytic streptococcus infection; in Cases 1 and 23, from whom this organism was also recovered, serologic evidence did not suggest that streptococcal infection played a part in their disease.

Cases in Which the Clinical Impression of Primary Atypical Pneumonia Was Erroneous or Not Established. Cases 2, 14, 16, 22, 25 and 26 were thought to have primary atypical pneumonia on admission. Of these, Cases 14, 16, 25 and 26 are of particular interest since all appear to have had pneumococcal pneumonia. These 4 patients were first seen relatively late in their illnesses and only 1 presented physical signs of pulmonary involvement. In 2, previous therapy had very probably altered the course of the disease, so that the patients did not seem particularly ill. Admission white blood counts of the 2 untreated patients (Cases 14 and 16) were 6.9 and 9 thousand, respectively. Case 25, who had received penicillin, had a white blood count of 17.6 thousand and Case 26, previously treated with sulfadiazine, a leukocyte count of 3.8 thousand. The appearance of these 4 patients' lungs in Roentgen ray films seemed of significance in retrospect, since all had hazy, rather evenly diffuse pulmonary shadows, which with 1 exception were located peripherally. This appearance is not in itself diagnostic, but differs from the common picture in primary atypical pneumonia. In each of these cases the provisional diagnosis was almost immediately made doubtful by the finding of significant types of pneumococci in the sputum. Direct identification of Type 7 (Case 14) and Type 4 pneumococcus (Case 16) was possible; in

the 2 previously treated patients pneumococci were recovered after mouse inoculation, Type 7 from Case 25 and Type 8 from Case 26.

In order to establish the rôle of pneumococci recovered from these patients with illnesses which deviated from the usual picture of lobar pneumonia, it was necessary to show that the patients had developed antibodies directed against the type of pneumococcus recovered. Cases 4, 15 and 26 developed agglutinins against their own organisms and did not develop agglutinins against a heterologous type (Type 1). Case 16 failed to develop agglutinins but did develop a significant level of mouse-protective antibodies against his own organism. In addition there was serologic evidence of concurrent influenza B in this patient.

Two remaining patients were thought on admission to be examples of primary atypical pneumonia (Cases 2 and 22). Case 2 had a severe paroxysmal cough, with inconstant râles at both lung bases on admission. There was no Roentgen ray evidence of pneumonia. He developed antibodies against influenza A virus, and was finally classified as influenza A with bronchitis of undetermined etiology. Case 22 had the clinical appearance of atypical pneumonia, with pneumococcus Type 43 recoverable from his nose, throat and sputum. His serum gave only negative results in all tests performed. The final diagnosis was pneumonia of undetermined etiology, but it is possible that this patient is actually an example of primary atypical pneumonia.

Résumé of Final Diagnoses. *Cases for Which a Single Infectious Agent Appeared Responsible.* In 10 patients (Cases 2, 3, 4, 8, 9, 10, 11, 12, 13 and 17), the bacteriologic and serologic findings suggest that one or the other of the influenza viruses was the sole etiologic agent involved. However, 5 of these patients (Cases 2, 3, 4, 11 and 12) showed localized râles, and 1 of these (Case 4), as well as in Case 17, there was Roentgen ray evidence of pulmonary infiltration. No additional evidence could be adduced to explain these lung findings.

Four patients (Cases 6, 15, 20 and 7) appear to belong in the primary atypical pneumonia group. Clinical and laboratory evidence in the first 3 causes them to be so classified, and the evidence suggests that Case 7, despite the absence of pneumonia in Roentgen ray films, belongs in this category.

In 3 patients (Cases 14, 25 and 26) pneumococcus appeared to be the sole etiologic agent. In 2 patients (Cases 18 and 22) the etiology remains doubtful.

Cases for Which More Than One Infectious Agent Appeared Responsible. In the remaining 7 patients the effects of more than 1 infectious agent must be considered. In 2 instances (Cases 19 and 24), although influenza virus infection appeared to be responsible for the clinical manifestations, there is evidence that concurrent infection by beta-hemolytic streptococcus occurred. In 1 instance (Case 16) concurrent infection by influenza B virus and pneumococcus Type 4 appears to have taken place. There is a further group of 4 patients (Cases 1, 5, 21 and 23) in which infection by an influenza virus and the agent or agents of primary atypical pneumonia appear to have occurred at approximately the same time, and in 1 of these (Case 21) infection by beta-hemolytic streptococcus also occurred.

Diagnostic Errors. On comparing the clinical impressions with the final diagnoses, as has been done graphically in Figure 1, two principal errors stand out. The first, an error of omission, was failure to suspect the rôle of the influenza viruses in many of these cases. This became evident, in most instances, only after serologic tests had been done, and was particularly striking in those patients with pneumonia which presumably was due to another agent. Multiple diagnoses are commonly viewed with suspicion, for it is well known that a single pathologic process may manifest itself in various organs in such a manner as to suggest that more than 1 disease is present. The present

studies indicate that what appears to be a single disease picture with involvement of a system, the respiratory tract, may be associated with infection by more than 1 infectious agent, and in most instances it is impossible to judge whether one or another of the agents plays a "primary" or "secondary" rôle.

The second principal error, one of commission, was the classification as primary atypical pneumonia of cases with other infections. This occurred most often with pneumococcal pneumonias which showed an atypical onset or course. It seems obvious that the similarities among acute respiratory tract infections of different

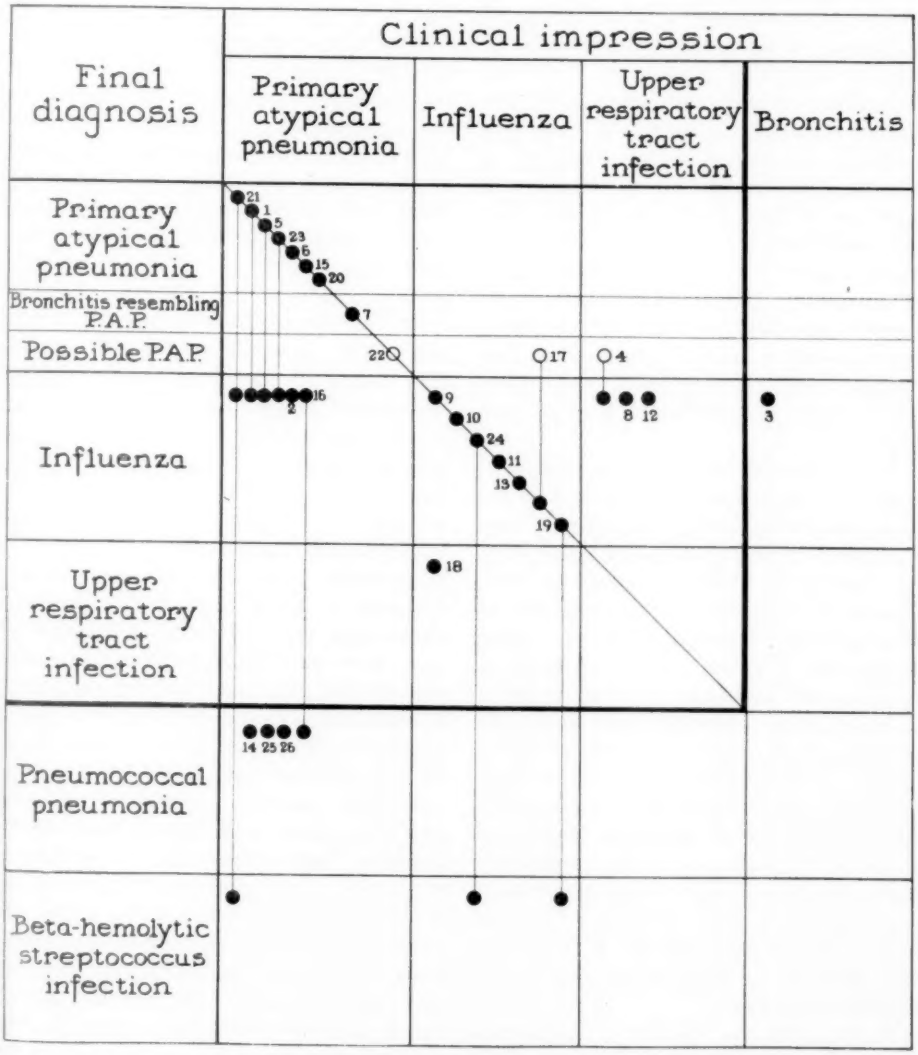

FIG. 1.—Graphic comparison of original clinical impressions with final diagnoses. Each numbered circle denotes a single patient. Each solid circle represents a single diagnosis, and solid circles connected by a vertical line represent multiple diagnoses in a single case. Clinical impressions confirmed by laboratory tests are represented by circles lying on the oblique line; circles distant from the line represent clinical errors of varying degree. Open circles represent cases in which positive serologic evidence for satisfactory classification was lacking.

etiologies are considerably more striking than the differences; although a correct diagnosis may be reached by clinical methods, such a diagnosis cannot be considered as established without a considerable amount of laboratory evidence.

Fashions in terms play their part in erroneous diagnosis and "primary atypical pneumonia" is a case in point. On clinical grounds alone a wide variety of different infections might be classified as primary atypical pneumonia. At the present time an accurate diagnosis in this disease rests largely upon the weight of negative evidence; *i. e.*, the exclusion of a number of specific infectious diseases, any one of which may closely simulate this condition. At the present time most workers agree that only 2 laboratory procedures, *e. g.*, cold hemagglutination and streptococcus MG agglutination, give positive assistance in the diagnosis of this disease, and yet it appears that either test is positive in not more than 50% of cases.

In the present state of knowledge of acute respiratory infections certain broad diagnostic terms might be applied to those conditions in which it is not possible or not feasible to establish a diagnosis with laboratory evidence. While the use of such terms as "catarrhal fever" or "upper respiratory infection" is indefensible if facilities are available for establishing a more accurate diagnosis, it is preferable to the use of "primary atypical pneumonia" or "influenza" when these diagnoses are not or cannot be substantiated. In the absence of adequate laboratory evidence the terms "acute respiratory tract infection" and "acute respiratory tract infection, with pulmonary involvement" are about as specific as the facts will allow in the great majority of acute respiratory ailments.

Importance of Correct Diagnosis. From the point of view of the patient accurate diagnosis is chiefly important as a basis for appropriate therapy. In acute respiratory infections there appears to be a tendency now to reverse the usual procedure and diagnosis is often dependent upon the effects of therapy. This is open to serious criticism, for aside from the hazards of adequate sulfonamide therapy and the difficulties and expense of adequate "antibiotic" therapy, there is the impossibility, when they are used blindly, of interpreting results, and the further real danger that diagnosis may be left to the academician. It has been suggested that therapeutic agents may in the future be developed, the range of efficacy of which may be so wide as to relegate diagnosis in certain infectious diseases to the class of a minor art. There is equally good reason to believe, however, that the further development of therapeutic agents may make available substances with a high degree of specificity, both in their therapeutic range and in their point of attack upon the infectious agent, and that their proper use may depend upon a diagnostic accuracy which has not yet been achieved with respect to acute respiratory tract disease.

Summary. The difficulties of accurate diagnosis in acute respiratory infections are brought out by relating in a group of such cases the clinical impression on admission with laboratory findings early and in convalescence, and with the final diagnoses arrived at after the accumulation of all the pertinent data. It is shown that concurrent infection by more than one infectious agent may occur often. It is suggested that in the absence of confirmatory laboratory evidence supporting a specific diagnosis, non-specific terms be used to describe acute respiratory infections. It is also suggested that modern therapeutic agents may require more, rather than less, diagnostic accuracy for their effective use.

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THE CHANGING CONCEPT OF MYELOMA OF BONE

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Myeloma is no longer considered an unusual disease. Over 1000 cases are reported in the literature on the subject. To add a series of 13 cases studied at Temple University Hospital merely to review the usual clinical, laboratory and morbid anatomical findings would add little of value to what is already known. But, whereas the disease today is probably no different than it was in 1850 when McIntyre first described it, in the last ten years there has been a very definite change in our concept. In 1928 Ewing[6] wrote, "Multiple myeloma is a specific malignant tumor of the bone marrow, arising probably from a single cell-type, and characterized chiefly by multiple foci of origin, a uniform and specific structure composed of plasma cells or their derivatives, rare metastases, albumosuria, and a fatal termination." Today we must admit that the tumor may possibly arise from extra-medullary sources, that it is probably not of a single cell origin, that it may have a single focus for a considerable period or it may be so diffuse that no foci are apparent and that it may be composed of other than plasma cells.

The change in our concept of this tumor involves principally (1) a better understanding of the subtypes, (2) its complex cytogenesis, (3) some recently developed laboratory diagnostic procedures and (4) the nature and kind of bone demineralization which it induces. The purpose of this discussion is to emphasize these aspects. The salient data concerning our cases are included not as case reports of an unusual disease, but to serve as a basis for the discussion.

Subtypes. Today we must recognize at least three subvarieties of this disease. The classical type occurs as multiple tumors arising in red marrow. They may occur simultaneously or successively over a period of months. Seven of our cases proved eventually to be of this type. The tumors occur preponderantly in flat bones and exclusively in areas where red marrow is found. In the age group most commonly affected (40 to 60 years) hematopoiesis is restricted to flat bones and the metaphyses. The tumor may rarely occur in younger patients.[15] Two in our series were under 40, one aged 32 and the other 16. In these two alone were the long bones affected. The remarkable lytic action of the tumor cells on the contiguous bone makes this type the easiest to diagnose. Indeed, the diagnosis may be made in many cases on examination of Roentgen-ray films of the flat bones.

A second subtype may begin as a single focus and remain solitary for a variable length of time. Reports of such cases are not uncommon.[4,11,14] Paul and Pohle[13] gave an excellent account of five such tumors. There has been a tendency to classify these separately under the heading of "solitary myeloma." There seems to be scant evidence, however, that the myeloma may exist in the solitary form indefinitely and so deserve a separate classification. All completely studied cases of a single lesion which we have encountered have eventually shown multiple foci. Four of our series were discovered in the single tumor stage. In three a single lesion was found in one of the lumbar vertebrae, in a fourth the tumor was located in the neck of the femur. All of these tumors became multiple within nine months.

A third subtype of myeloma appeared to be so generalized that practically all red

marrow is affected simultaneously. It is this type which produces generalized skeletal demineralization and consequemt profound changes in the peripheral blood. Two of our cases were of this nature. It was these cases which aroused our interest in this subject since both cases were misdiagnosed on the original Roentgen-ray studies as idiopathic senile osteoporosis. Both were in elderly patients and both showed marrow replacement by tumor plasma cells throughout the flat skeleton. Any of the above varieties may produce soft tissue metastases in the later stages of the disease, but these are usually found to be extra-medullary extensions rather than true metastases. However, unquestionable soft tissue tumors have been reported though these are exceptional.

Another type of tumor which probably is better designated as myelocytoma rather than myeloma is solely or predominantly confined to soft tissues. Hellwig[9] gives an excellent review of 127 such cases and Esposito and Stout[5] add one of their own. They were found predominantly in the upper respiratory passages and the conjunctiva with a few in the small intestine. There is considerable uncertainty among morphologists as to whether this type represents a separate tumor entity or whether it should be considered a subvariety of the marrow type. Its behavior is completely different since its growth is phlegmatic and it may be cured by complete removal. Though its component cells are impossible to distinguish morphologically from some of the marrow tumors its clinical features are so different that it seems best to exclude it from this discussion.

Cytogenesis. The cytogenesis of myeloma is still poorly understood. It is now certain that the plasma cell myeloma is but a single, though the most common, type. A number of excellent papers have appeared recently presenting evidence of the protean genesis of this group. Some writers believe that young forms of both the myelogenous and erythropoietic series may assume neoplastic propensities and produce myelomas of a particular cell type. Herbut and Erf[8,10] have recently described tumors which behaved like myelomas and which they believed to arise from megakaryocytic and lipoblastic marrow elements. One is reminded of the dangers in hypothesizing on tumor cell origins on the basis of static morphology alone. While such a concept seems startling, if we accept the hypothesis that all marrow elements are of mesenchymal origin along with the fibrous, cartilaginous and bone tissue, one is forced to admit that such tumors, at least the megakaryocytoid type if such a tumor exists, could be classified as a myeloma in its broadest sense. In such a classification the Ewing's tumor might also belong in the myeloid group. Its clinical features are not too dissimilar except in regard to the age group affected. Its cytology is certainly consistent with a marrow origin and its site of predilection is explained by the red marrow distribution at this age.

In short, the number of these various tumors of marrow cells included under the heading of "myeloma" depends upon the inclination of the writer. From the clinical standpoint the entire group may be considered together. They begin in the marrow of flat bones and long bones in young patients and almost exclusively in flat bones in the older group. They may be single at first but eventually become multiple. They show varying degrees of lytic action on bone and, in all, the eventual prognosis is hopeless.

From the cytomorphologic standpoint there are but two clearly defined types, the plasma cell myeloma and the Ewing's tumor. This leaves a considerable number which can be differentiated on the basis of cytologic character alone. It is agreed by all that these tumors arise from various of the marrow elements; it is unfortunate that the limitations of microscopic study prevent us from knowing exactly which one. One feature of interest is brought out by examination of aspirated sternal marrow. Such material from 5 of our cases was studied. One showed no mye-

loma cells. Of the other 4, two were of the myeloid and 2 of the plasma cell type as diagnosed on sectioned tissue taken directly from the tumors. Yet, in all 4 instances the marrow smears showed nearly identical tumor plasma cells. Seven of our series were of the classical plasma cell variety, while 6 were "myeloid" in type.

Lowenhaupt[12] and others consider the plasma cell type to arise from the reticuloendothelial elements of marrow and elsewhere, particularly the spleen. This concept makes myeloma a diffuse process which in a sense is comparable to the leukemias. In the three cases of our series which were autopsied there were abnormal numbers of plasmocytes in the splenic sinuses and some of these were multinucleated. Two of these spleens were smaller than normal, while only one was enlarged (300 gm.).

LABORATORY PROCEDURES. Many cases of myeloma develop signs and symptoms of kidney insufficiency. There has been great controversy concerning this complication. Some writers contend that the passage of Bence-Jones protein caused glomerular damage with resultant functional impairment, but Bell,[1] and Forbus[7] et al. have described the kidneys of myeloma cases and attempted to produce kidney damage experimentally by forced excretion of this material. Both are definite in their statements that the protein acts only as foreign body casts which block the tubules. Ehrich described this tubular obstruction by Bence-Jones protein casts and applied the term "internal hydronephrosis." This explanation of renal insufficiency seems logical except that no mention of anuria or oliguria is made, and if the damage is dependent on mechanical fluid obstruction, it would seem that curtailed urine excretion would of necessity be a symptom. Of our 3 autopsied cases, cast formation was marked in one, slight in another and entirely lacking in the third. Bence-Jones protein was found in the urine of none of these patients, though admittedly it may have been transient and lacking only at the time at which the test was made. Of these 3 cases only the one with casts suffered from impaired renal function. But at no time was there a subnormal urine output, though there was a consistent cloud of albumin. One is led to wonder if the casts in the tubules in this patient were artefacts, the result of the coagulating action of the fixative upon the increased protein in the fluid urine. The glomeruli showed a fibrinoid type of degenerative change which may have accounted for the functional disturbance.

It is generally believed that the Bence-Jones protein is derived from the myeloma cells and/or the cells of normal bone marrow. Its excretion through the glomeruli is partially explained on the basis of its molecular weight which is about half that of serum albumin, although another factor is apparently involved. It is predominantly a beta globulin.[2] The reticulum and at least some of its derivatives are active in the formation of globulin and in antibody production. The association of increased plasma globulin and the presence of abnormal numbers of plasmocytes is encountered in numerous diseases. It would seem possible that the type and the increase in amount of the globulin present in some cases of myeloma may depend upon the type of marrow cell from which the tumor derives. Whatever the cause of the renal insufficiency, chemical examination of the blood and urine should be made in all cases suspected of myeloma. If protein is present in the urine it should be examined for Bence-Jones bodies.

Bence-Jones protein is probably not as commonly present as the earlier accounts would lead one to believe, or it may be transient and missed on one or even more analyses. Most recent accounts give an incidence considerably below the 73% originally reported. It was looked for in 12 of our cases but found in only 1. However, large amounts of albumin were found in 3 others. Hyperproteinemia was found in 3, hyperglobulinemia in 2 (examined for in only 5) and hypercalcemia in 3. In 10 cases a definite anemia was present and in

FIG. 1

FIG. 1

Case	Sex	Age	Subtype	Cell Type	Area	Serum Calcium (mg. per 100cc.)	Serum Phosphorus (mg. per 100cc.)	Total Protein (Gm. per 100cc.)	Albumin (Gm. per 100cc.)	Globulin (Gm. per 100cc.)	R.B.C. (Million)	Sedimentation Rate (mm.perhr.)	Leucocytes	Urine Albumin	Bence-Jones Protein
1	M	60	Diffuse	Plasma Cell	All Red Marrow	13	5.2	7.3	5	2.3	3.5	..	14,600	Moderate	0
2	F	63	Diffuse	Plasma Cell	All Red Marrow	9.2	4.1	9	3.5	5.7	1.2	..	14,900 Young Forms	Heavy	0
3	M	64	Solitary then Multiple	Plasma Cell	Vertebrae and Flat Bones	12.6	3.7	6.8	...	...	1.7	..	250 Young Forms	Trace	0
4	F	59	Solitary then Multiple	Plasma Cell	Vertebrae	18	2.6	6.5	4.8	1.7	3.5	18	14,000	Trace	0
5	M	45	Solitary then Multiple	Plasma Cell	Vertebrae	11.4	4.2	...	...	...	1.7	38	8,400	Heavy	+
6	F	32	Solitary then Multiple	"Myeloid"	Femurs Ilium	...	...	...	...	...	4.4	..	17,000 Young Forms	Trace	0
7	F	42	Multiple Focal	"Myeloid"	Femur Skull	10.3	4.1	...	...	...	3.8	..	10,000 Young Forms	0	0
8	M	62	Multiple Focal	"Myeloid"	Flat Bones	...	...	9	...	...	2	..	8,400 Young Forms	Trace	0
9	F	68	Multiple Focal	Plasma Cell	Vertebrae Pelvis	...	...	...	...	...	...	..	....	....	0
10	M	40	Multiple Focal	Plasma Cell	Flat Bones	11	4.8	7.5	...	...	2.4	..	7,700	Heavy	Not Examined
11	M	55	Multiple Focal	"Myeloid"	Flat Bones	10.5	7 2	...	...	...	2.8	..	7,900	Heavy	0
12	F	16	Multiple Focal	"Myeloid"	Flat Bones	11.4	3.7	6.6	3.7	2.8	2.7	24	20,000 Young Forms	Moderate	0
13	F	56	Multiple Focal	"Myeloid"	Ilium Skull	...	...	8.1	4.9	3.2	4.3	..	7,200	0	0

FIG. 1.—An X-ray film of the lumbar spine of a patient with the uncommon solitary focal type of bone demineralization. There is a spherical defect in the body of the second lumbar vertebra.

FIG. 2.—An X-ray film of the lumbar spine of a patient with diffuse myelomatosis. There is loss of stature of the vertebral bodies and biconcave deformities. This appearance may be mistaken for "senile" osteoporosis.

8 it was severe enough (from 1.2 to 2.8 million r.b.c.) to constitute an outstanding sign. Leucocytosis, young myeloid forms and Türk cells which are sometimes found in the peripheral blood are produced in other diseases which affect the marrow, probably the result of irritation. All but 3 in our series showed these phenomena. An increase in the sedimentation rate was found in the 3 cases in which the test was made. This is probably a non-specific reaction, since the sedimentation rate is increased in hyperglobulinemia.

If the myeloma process is a solitary lesion a needle biopsy may give tangible evidence of its true nature. Needle biopsies of bone are not as difficult as most clinicians seem to believe and in the case of the myeloma where there is Roentgen-ray guidance and cortical destruction they are particularly easy. A positive diagnosis was made on the only one of our series on which it was tried. In such instances the usual aspiration needle may be used but it is possible to get through a rather heavy compacta with a needle of the Turkel type. The tumor cells, if properly treated, are not difficult to interpret by the pathologist because of their distinctive morphology.

Bone Lysis. While pathological fracture is given in most accounts as the most constant sign of the disease,[8] bone pain almost invariably occurs first, and if properly interpreted a much earlier diagnosis can be made. It is quite true, as pointed out by Geschicter, that pathological fracture of a flat bone is apt to mean destruction by myeloma because most other osteolytic processes are more likely to involve cylindrical bones, but back or chest pain with focal tenderness almost invariably precedes the fracture by months. It may be argued that the symptom of back pain is so common in the myeloma age group that it is almost worthless as a diagnostic aid, but, if patients with this symptom were thoroughly studied from the outset, it would mean in almost every instance an economy of money and time for both patient and physician. Nine of our patients complained of back pain as the initial and outstanding symptom and the other four gave a history of pain in the affected bone.

In many instances a Roentgen-ray film of the involved skeletal part will suggest the diagnosis of bone destruction by malignant neoplasm. An original diagnosis was so made in 5 of our series, and in only 2 cases did the first roentgen examination fail to reveal presence of bone disease. The Roentgen-ray cannot always define the cell type of the tumor, but such a diagnosis points the way to further laboratory study which should eventually fix the correct nature of the lesion. It is unfortunate that in a certain number of myeloma cases the demineralization is so diffuse that unless the radiologist and clinician are aware of this possibility a diagnosis of osteoporosis may be made. Two of our 13 cases were so classified. On one of these the diagnosis of diffuse myeloma was made later by biopsy and the other came to necropsy before the true nature of the disease was suspected. With the complaint of flat-bone pain and a Roentgen-ray description of generalized demineralization, the clinician must not be satisfied with a diagnosis of senile osteoporosis until sternal marrow smears have been examined and other diagnostic laboratory procedures performed.

If the tumor is of the generalized type which produces this picture in the majority and perhaps in all cases, a marrow smear, usually from the sternum, may present myeloma cells. This procedure is so simple that one wonders why it is not universally applied where myeloma is suspected. If the diagnosis of diffuse myeloma cannot be sustained, then other causes of generalized demineralization may be considered. These are carcinomatosis, hyperparathyroidism (rare), osteomalacia (rare in this country), osteoporosis secondary to renal insufficiency, osteoporosis due to hyperthyroidism, rarely tuberculosis or Gaucher's disease and finally idiopathic senile osteoporosis.

In conclusion it should be emphasized that an early diagnosis of myeloma can be made if the symptoms of bone pain are considered sufficient reason for Roentgen-ray study. If focal or generalized demineralization is so demonstrated, the diagnosis can be made or ruled out by marrow smear and study of the blood and urine. As a last resort aspiration or open biopsy may be tried on a focal lesion. Cases of

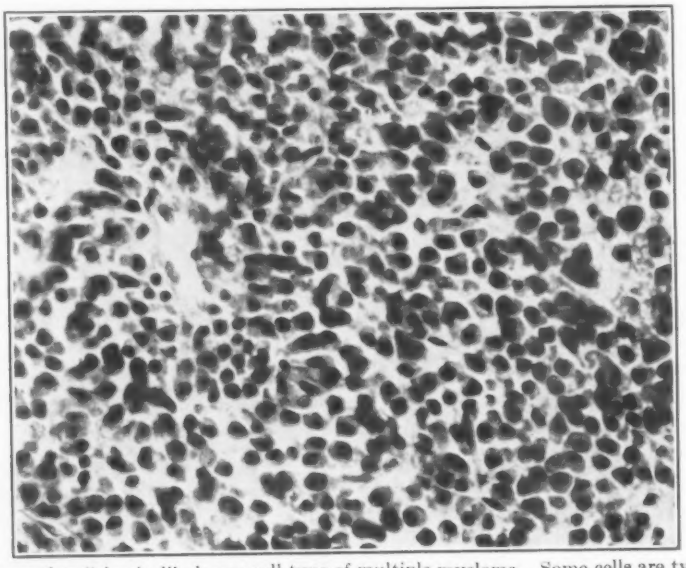

FIG. 3.—The usual or "classical" plasma cell type of multiple myeloma. Some cells are typical plasmocytes. Others appear to be young forms of the same type.

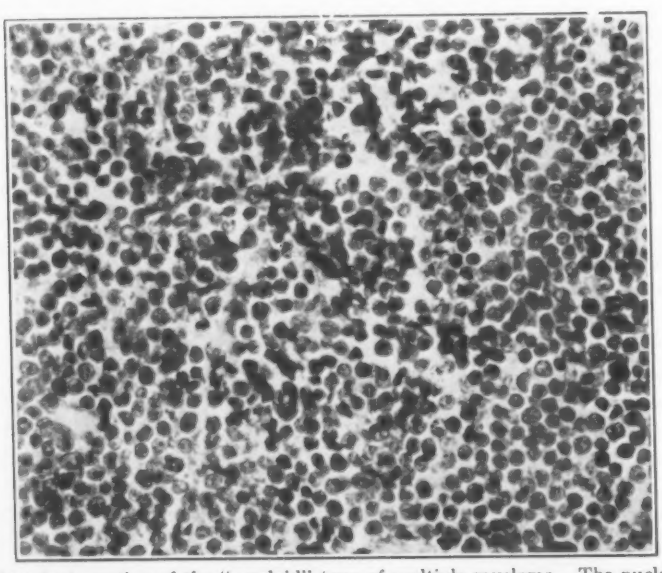

FIG. 4.—A histologic section of the "myeloid" type of multiple myeloma. The nuclei show greater disparity in form and chromatin content. None of the cells can be identified as plasmocytes.

generalized demineralization should not be diagnosed as idiopathic senile osteoporosis until these studies have been carried out.

Summary. There are four main points which need emphasis in considering myeloma of bone.

1. There are three clinical subtypes: that which begins as a single focus, but eventually becomes multiple; the classical multicentric tumor; and the diffuse type which involves all the red marrow simultaneously. The rare extra-medullary type acts quite differently and should not be included in this group.

2. Myeloma is a group of tumors of which the plasma cell is only one type. They all arise from marrow elements and they all behave similarly.

3. Severe back pain or persistent bone pain of obscure origin warrants Roentgen-ray examination. If demineralization is found, there are a number of laboratory procedures which are helpful in establishing a diagnosis of myeloma. The urine should be examined for signs of renal disease and Bence-Jones protein. The blood should be analyzed for increased globulin. A sedimentation rate may be helpful. Sternal marrow should be aspirated and examined for myeloma cells.

4. It should be remembered that all the marrow may be involved diffusely, and so a patient with evidence of generalized bone demineralization should not be dismissed with a diagnosis of idiopathic senile osteoporosis.

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DISSEMINATED CALCIFICATION OF THE PANCREAS: SUBACUTE AND CHRONIC PANCREATITIS

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The purpose of this paper is to draw attention to the least frequently recognized form of pancreatic lithiasis, known variously as disseminated calcification of the pancreas, pancreatitis petrificans and diffuse parenchymal calcification of the pancreas, and to add two reports of cases to those now existing in the literature. An attempt will also be made to stress the clinical picture which should aid in its more frequent recognition in the future, to suggest the relation of the condition to other forms of pancreatitis, and to discuss its treatment.

It was Beling[3] who first suggested, in 1940, that a distinction should be made between disseminated calcification of the pancreas and the usual form of pancreatic lithiasis. In the former condition he suggested that a variable portion of the parenchyma of the gland is replaced by calcium deposits and in the latter the ducts contain single or multiple stones. He collected 12 cases of calcification of the pancreas from the literature, and credits Allen[2] with describing the first in 1903. From a study of this group, and an additional case of his own, Beling describes a clinical picture and a characteristic history.

King and Waghlstein[6] reported four additional cases in 1942; one additional patient each is reported by Pascucci,[8] Sage,[10] and Thannhauser[11] and 2 by Wechsler and Weimer,[12] bringing the total number of cases in the literature prior to this report to 22. While the patients described by the two last mentioned authors were not classified as disseminated calcification of the pancreas, but simply as pancreatic lithiasis, we feel that the symptomatology, laboratory studies and Roentgen-ray findings are sufficiently typical to warrant reclassification.

The incidence of pancreatic lithiasis in general is not high. The aggregate figures from ten pathological laboratories showed only 31 cases among 117,031 routine necropsies or 0.044%.[8] However, the reliability of these statistics is questioned by the work of Ludin[7] who, after a preliminary roentgenogram of the pancreas at postmortem, dissected all the glands showing heavy shadows and demonstrated stones in 28 out of 542 organs, or 5.5%.

Etiology. The cause of disseminated calcification of the pancreas is not known but is thought to result from repeated attacks of acute or subacute pancreatitis occurring in adult life. Consequently the theories regarding the etiology of acute pancreatitis, such as bile regurgitation, infection or metaplasia of the ducts with consequent obstruction, are equally applicable here. It seems to us that it may also be possible that this condition is the result of chronic pancreatitis originating in childhood, since disseminated calcification of the pancreas has been found to occur in patients as young as 17 years, symptoms frequently date back to childhood and the characteristic features of abdominal pain, weakness, malnutrition, icterus and steatorrhea are common to both. Cole and Howe[5] describe a similar syndrome occurring in patients with pancreatic atrophy associated with fatty degeneration of the

liver and claim this syndrome is similar to that found in children with chronic cystic fibrosis of the pancreas.

PATHOLOGY. Detailed pathologic studies of the pancreas in cases of disseminated calcification are not numerous. The majority of patients in whom this condition has been diagnosed have not had histologic section of the pancreas made; instead, the diagnosis was made by gross examination of the gland at operation or autopsy, or as a result of roentgenogram. Grossly the gland is firm, showing beneath the capsule numerous fine, hard, white bodies. Upon cutting, these are noted to be calcareous deposits, and the finer ducts are dilated and seen to contain minute calculi removable with a needle. Those cases in which histological examination has been made showed the presence of extensive inter- and intra- lobular fibrosis and considerable mononuclear cell infiltration. The parenchyma of the gland was largely replaced by this fibrosis, and those acinar cells remaining were normal in appearance except in those areas where there was marked intra-lobular fibrosis. When the fibrosis is particularly extensive it may encroach upon, and replace, the islet cells, but usually these remain intact in spite of the wide-spread acinar replacement. The larger ducts show a variable degree of dilatation and minute calculi are seen to extend from here through the smaller ducts and into the finest acini; however, they do not appear to impinge upon or replace the actual secreting cells.

In 6 of the 15 patients with disseminated calcification of the pancreas who were operated upon or observed at necropsy, stones were found in the larger ducts in addition to the calcification present in the parenchyma. It would seem likely that the diffuse gritty sensation observed on cutting into the gland and the diffuse infiltration noted upon Roentgen examination might be the result of very fine radicles of the pancreatic ducts being almost completely filled with deposits of finely granular calcium salts. If this is true it would suggest that the deposition of calcium is simply a progressive phase of the condition causing the deposit of pancreatic calculi in the larger ducts. However the outstanding histologic feature is the marked interlobular fibrosis and the atrophy or replacement of acinar tissue. In this respect there is marked similarity in the histology of this disease to that of the pancreatic atrophy of Cole and Howe's patients and chronic cystic fibrosis in children.

SYMPTOMATOLOGY. In the 24 reported cases there were 20 males and 4 females; 22 of whom were white and 2 colored. The average age was 38.6 years; the youngest patient was aged 17 years and the eldest 76.

The outstanding symptom of which these patients complain is some form of abdominal pain, usually existing over a period of months or years. In some patients the onset of symptoms could be traced back to childhood. The pain varies greatly in severity and location. It is usually of a gnawing, boring type, occasionally described as knife-like. It is most frequently present in the epigastrium, going through to the back, but may also radiate to the right or left hypochondriac regions, the pelvis or either shoulder. The episodes of pain may vary considerably in length, and are usually not related to meals. However, particularly severe attacks may arise following an excessive intake of alcohol. Nausea, bloating, anorexia and vomiting are frequently present. The pain may be relieved by taking sodium bicarbonate but more frequently it requires morphine. Steatorrhea and creatorrhea are present in about 25% of the patients. When this exists for any length of time, weakness and loss of weight may be pronounced. In the 24 cases reported transient jaundice with enlargement of the liver was present in 8 cases; diabetes in 2 cases; in 9 cases a history of excessive indulgence in alcohol was obtained; 3 patients had an associated pulmonary tuberculosis and 3 had syphilis.

LABORATORY FINDINGS. The most important laboratory finding is an absent or

diminished pancreatic secretion. It is now generally felt from the work of Agren and Lagerlof,[1] that considerable information regarding pancreatic function can be obtained from the secretin test.

This is carried out by introducing a specially designed double-lumened tube into the stomach and duodenum, which permits aspiration of the gastric and duodenal secretions simultaneously. When a basal level of duodenal juice is obtained the secretin is injected intravenously. Normally there is a prompt increase in the volume of the juice and in its bicarbonate and enzyme content. A marked reduction in volume and in bicarbonate and enzyme content is indicative of abnormal pancreatic function. There are other methods of stimulating the pancreatic secretion, such as injecting mecholyl, which stimulates the vagus and thereby increases the enzyme content but has little effect on the volume; and the introduction of hydrochloric acid or ether[4] into the duodenum is thought by some to cause an increase in the pancreatic secretion similar to that produced by secretin but of less intensity. We have employed the latter method because secretin was not available commercially and the untoward side effects that occur at times with mecholyl made us feel that this procedure was contraindicated in an already sick or weakened patient.

Stool Examination. If steatorrhea is present the stool grossly is large, mushy and formless; if collected in a pan and allowed to stand for a while the free fat will separate and run off in small streams. The odor is fetid, but there is not much frothing or bubbling of gas; the color is light tan, and glistens due to the fat. Microscopically a great increase in oil droplets is readily discernible, and staining with Sudan 111 brings this out strikingly. Creatorrhea, or the presence of striated muscle fibres in the feces, is characteristic and easily recognized in simple wet microscopic preparations. Chemical analysis for total fat will show a considerable increase over the normal amount, but further analysis for the partition of neutral fat and fatty acids hardly seems to aid much in differential diagnosis since it is now generally recognized that free fat can be eliminated in the stool both in diseases of disturbed intestinal absorption and pancreatic insufficiency.

Urinalysis. Routine urinalysis shows little when the condition is primary, but during acute episodes and in the presence of marked wasting a variable degree of albuminuria may develop.

Blood Count. This ordinarily shows a normal number of leukocytes and a slight normocytic anemia, but during acute episodes there may be a moderate leukocytosis.

Blood Chemistry. This likewise varies little; the serum amylase is usually within normal limits, but may be elevated during an acute episode; the blood cholesterol is low normal or at times definitely reduced, and blood sugar is normal.

In patients who have developed a secondary diabetes, glycosuria and a typical diabetic curve in a glucose tolerance test will be obtained.

Liver Function Test. When jaundice is present it is usually mild. The available data show that the qualitative van den Bergh reaction is positive direct and the quantitative reaction shows a slight elevation. There may be some retention of bromsulfalein and an increase in the alkaline phosphatase activity.

Roentgen Examination. The typical Roentgen picture in disseminated calcification of the pancreas shows a diffuse, stippled calcification involving the head, body and tail. This has been observed to take place within an 18-month period in 1 case, and in another a progression has been observed beginning in the head, going through the body and reaching the tail within 7 years. While the finding of typical calcification of the pancreas on Roentgen-ray examination, when the condition is advanced, will rarely permit of misinterpretation, it should be borne in mind that the degree of calcification may be minimal and not necessarily in propor-

tion to the severity of the symptoms. In addition, unless a plane film of the abdomen is made, the calcification of the pancreas that is present may be obscured by the materials used in conducting some other examination such as a gastrointestinal series, cholecystogram, barium enema or pyelogram. Even if the calcification is noted upon Roentgen-ray examination it may be looked upon as a coincidental finding and no importance attached to it; it should be stressed that with such Roentgen-ray finding, although symptoms are minimal and not attributed to pancreatic dysfunction, the possibility of the future development of symptoms is great. Additional Roentgen-ray findings that may be of aid in evaluating this condition are the typical deficiency pattern of the small bowel described by Golden and the granular appearance of the small bowel contents resulting from a mixture of feces and free fat.

DIAGNOSIS. In any patient with a long history of upper abdominal pain the possibility of disseminated calcification of the pancreas should be considered. Subsequent confirmation of the diagnosis is then dependent upon: (1) a plane film of the abdomen including that area between the 1st and 4th lumbar vertebrae; (2) stool examination for total fat and creatorrhea and (3) pancreatic function test.

It should be borne in mind that this condition may simulate many other chronic diseases of the abdomen but that the character of the pain is usually of a gnawing, boring type, going through to the back, frequently on the left. When the roentgenogram, stool examination, and pancreatic function test are carried out there will usually be found definite roentgenographic evidence of calcification in the abdomen, steatorrhea, and creatorrhea in the stool and a reduction in the pancreatic secretion, if disseminated calcification of the pancreas is present.

The disease with which this condition is most commonly confused is some form of biliary tract disturbance, usually cholecystitis. However, if the character of the pain, and the long history, frequently going back to childhood, are kept in mind, pancreatic involvement will be diagnosed more frequently. Differentiation should be able to be established by carrying out the studies referred to above.

Similarly, peptic ulcer is another lesion that gives rise to symptoms in the right upper quadrant; both pancreatitis and ulcer are associated with nausea and vomiting and pain that may be relieved with alkalies. However, the pain associated with the pancreatic lesion is not so rhythmical, is less related to food and is usually located on the left side, as well as on the right. The presence of occult blood in the stool, gastric analysis and gastrointestinal Roentgen-ray should be sufficient to diagnose the ulcer.

Perforated viscus may be suspected when the patient is having a particularly severe attack of pain; the recti muscles may be extremely hard and vomiting and prostration pronounced. If there is an accumulation of air under the diaphragm diagnosis will not be difficult, but in its absence differentiation may not be possible until the acute symptoms have subsided.

Renal lesions are apt to be suspected if the pain extends into the pelvis or follows down one of the ureters; this is more apt to occur on the left as a result of the tail of the swollen, enlarged pancreas coming into contact with the ureter. Hematuria and left lumbar pain are in favor of the renal involvement, but the absence of pyuria or renal calculus should stimulate further search for the cause.

TREATMENT. The relief of the acute symptoms usually requires the administration of morphine, while simple sedatives and rest will carry the patient through the milder attacks. When the condition is far advanced and a true pancreatic insufficiency is established causing steatorrhea, weakness and cachexia, it can be benefited by a low-fat, high-caloric diet, vitamins and large doses of Pancreatin. Vitamins A and D would appear to be indicated because of the failure of absorption that existed during the pancreatic

deficiency state. Pancreatin should be given in triple strength in enteric-coated pills, and the dosage should be gauged according to the response in weight gain and the reduction in steatorrhea. In some patients 8 gm. daily has been recommended to accomplish this.

Although there has been surgical removal of stones in the larger ducts of the pancreas associated with disseminated calcification, there is no evidence that this has materially changed the course of the disease. Recently partial and total pancreatectomies have been performed in selected patients with intolerable pain and threatened morphinism. The extent of pancreatic removal was the extent of involvement of the organ with calculi and calcification.[13]

We wish to describe 2 patients with disseminated calcification of the pancreas; the first we diagnosed during his latest admission. The second patient was not seen by us but was included because it is the only other instance of this condition that we could find after a search of the clinical, pathologic and Roentgen-ray files at the hospital.

Case Reports. CASE 1. F. A., white, male, aged 33, occupation, miner. We first saw this patient when he was admitted to the hospital in February, 1946, at which time

TABLE 1.—LABORATORY FINDINGS IN CASE 1, F. A.

Admission	First	Second	Third	Fourth	Fifth	Sixth
Hemoglobin	94%	71%	70%	45%	79%	90%
RBC	4,200,000	3,200,000	3,500,000	2,500,000	3,500,000	4,100,000
WBC	13,600	4,000	10,000	11,400	14,200	6,300
Wassermann	negative	....	negative	negative	negative	negative
Urinalysis:						
Albumin	one plus	negative	two plus	negative	negative	negative
Sugar	negative	negative	negative	negative	negative	negative
Stool Examination	....	....	....	....	positive for occ. blood No excess fat, ova or parasites present	1. Many fat globules. 2. Fat 42% dried wt. 3. Fat 23% dried wt. 4. Fat 18% dried wt.
Retention of Bromsulfalein	none	....	....	10%	none	none
van den Bergh:						
Qualitative	negative	....	....	positive	negative	negative
Quantitative (mg. per 100 cc.)	0.3	....	....	1.7	0.6	0.4
Urobilinogen	....	....	....	positive 1–50	....	....
Cholesterol (mg. per 100 cc.)	94	....	....	366	124	158
Ester (mg. per 100 cc.)	62	....	....	288	104	121
Free (mg. per 100 cc.)	32	....	....	78	20	37
Protein (gm. per 100 cc.)	6.76	....	6.14	....	6.65	5.8
Albumen (gm. per 100 cc.)	3.83	....	3.64	....	4.81	3.5
Globulin (gm. per 100 cc.)	2.93	....	2.5	....	1.84	2.3
Urea Nitrogen:						
BUN (mg. per 100 cc.)	8.95	....	....	....	....	9.8
NPN (mg. per 100 cc.)	18	....	29	22	....	....
Prothrombin time	....	....	....	....	100%	....
Serum Amylase	....	....	....	....	....	less than 80 units
Gastric Analysis:						
Total acid	57 units	....	....	....	....	45 units
Free acid	41 units	....	....	....	....	25 units

Glucose Tolerance Curve (Sixth Admission).
Fasting: 126 mgs. %; 1st hr. 147 mgs. %; 2nd hr. 85 mgs. %; 3rd hr. 60 mgs. %; 4th hr. 65 mgs. %; 5th hr. 77 mgs. %; 6th hr. 72 mgs. %.

he was complaining of an upper respiratory tract infection, abdominal pain and diarrhea. We found that he had been admitted on 5 previous occasions during the past 7 years, with complaints of upper abdominal pain.

His first admission was on March 19, 1939. His past medical history revealed that he had had no serious childhood illnesses; his appendix was removed in 1934; he had a soft chancre which was treated as syphilis, in 1938 and in November, 1938, he had a cholecystectomy for "hydrops of the gall-bladder" at another hospital. This latter operation was complicated by a post-operative atelectasis. For many years he had been a heavy drinker, consuming a pint to a pint-and-a-half of whiskey daily.

At the time of this admission the patient was complaining of upper abdominal pain radiating through to the right shoulder blade, intermittent nausea and vomiting for the past nine months. During this time he had

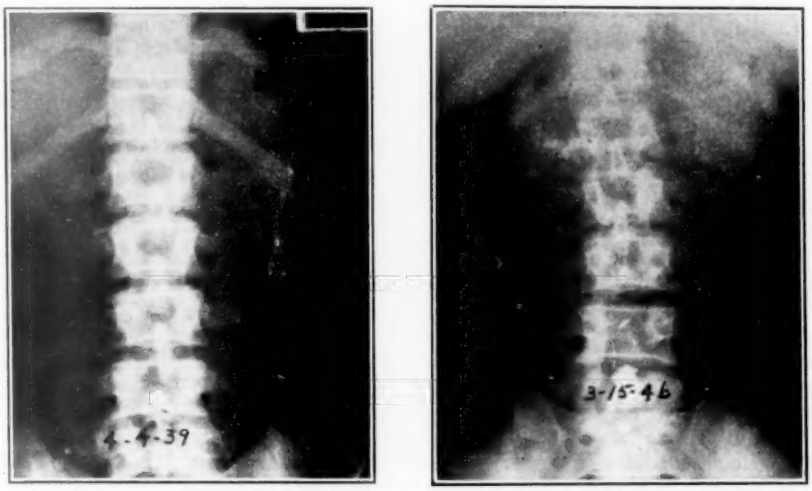

FIG. 1.—*Case 1.* Roentgenogram showing the progression in pancreatic calcification from 1939 to 1946

FIG. 2.—*Case 1.* Roentgenogram showing small bowel deficiency pattern.

FIG. 3.—*Case 1.* Roentgenogram showing granular appearance of ileum due to mixture of free fat and feces.

had some diarrhea and lost 50 pounds in weight. He had previously had constipation for a "long time." The patient states that these complaints were not relieved by the cholecystectomy in 1938, in fact he thinks they were aggravated.

Upon physical examination the patient did not appear to be acutely ill. The only positive finding was tenderness upon deep palpation in the right upper quadrant. The liver was enlarged and tender and the edge fairly smooth and sharp. A cholecystogram, taken because there was some doubt as to whether the gallbladder had been removed, showed no evidence of biliary calculi, but calcification was noted in the right upper quadrant just adjacent to the body of the first transverse process. This same calcification was again noted upon two additional Roentgen examinations. Exploratory laparotomy was performed and a large mass was found firmly adherent to the under side of the liver, from which several loops of small bowel were dissected. The great thickness of the adhesions was thought by the surgeon to be due to a suppurative process following the cholecystectomy. The pancreas was noted to be hardened in its entirety. Postoperatively the patient developed a sub-hepatic abscess which was drained. He recovered and was discharged from the hospital on June 15, 1939.

During the succeeding 2 years the patient was re-admitted to the hospital on 4 separate occasions at intervals varying from 1 to 7 months. The symptoms of which he complained during this time were similar to those he had upon his first admission, namely, a gnawing, boring pain in the epigastrium, radiating through to the back, which was not related to food, and only relieved by opiates, nausea, vomiting and loss of weight.

On the first of these admissions he was treated symptomatically; on the next admission there were clinical and Roentgen findings suggestive of pyloric obstruction for which a gastroenterostomy was done. On the third admission transient jaundice was present and thought to be due to a stone in the common duct which had passed, and on the fourth admission, because of the patient's continued complaints without demonstrable organic cause, a psychiatric consultation was held and a diagnosis of constitutional psychopathic state was made.

In April, 1944, he was operated upon at another hospital for a herniated intravertebral disc.

On February 2, 1946, 5 years after his last admission, he was admitted for the sixth time, with a primary complaint of upper respiratory tract infection of 3 weeks' duration. In addition, for the past 18 months he had been having intermittent attacks of sharp, colicky peri-umbilical pain radiating to the left flank, groin, scrotum and inner aspect of the thighs. These attacks occurred about once every 2 to 3 months and lasted about 2 weeks. During the attacks, and with heavy coughing, vomiting was frequent. The patient states he often induced vomiting which relieved the nausea and partially relieved the pain. For the past 2 or 3 years he had been having 11 to 12 stools daily. These frequently followed meals and contained undigested food and oily liquid. Physical examination revealed dry, wheezing and coarse, crackling râles throughout both lung fields, and the liver was enlarged three fingers' breadth below the costal margin. The temperature was 101.4 F., there was no icterus and no abdominal tenderness. Microscopic stool examination showed many fat globules and undigested striated meat fibers. The chemical analysis showed fat to be 42% of the dried weight. On 2 pancreatic function tests, no trypsin was present in any of the fractions obtained following stimulation with ether. The absence of pancreatic trypsin was confirmed on August 16, 1946, in a secretin test performed by one of us (W. J. S.) and Dr. M. H. F. Friedman. The volume response was within normal range but no trypsin was detected in any of the duodenal drainage samples.

A gastrointestinal Roentgen-ray revealed no evidence of abnormal lesion in the upper gastrointestinal tract except for moderate changes indicative of small bowel deficiency pattern and a granular appearance that was thought to be due to an admixture of free fat and the barium. A roentgenogram of the abdomen revealed diffuse calcification of the pancreas, and one of the chest showed accentuated hilar shadows with increased pulmonary markings radiating to both bases.

On bronchoscopic examination there was edema and redness of the bronchi and the presence of thick, tenacious mucus was noted.

On the basis of the calcification and the

small bowel pattern seen upon Roentgen-ray examination, the steatorrhea and creatorrhea, and the absence of trypsin, a diagnosis of disseminated calcification of the pancreas with pancreatic insufficiency was made. Treatment was instituted by giving the patient a low-fat diet, vitamins A and D, and Pancreatin. Initially 15 grains of Pancreatin were given daily, but it was only after this was increased to 90 grains daily

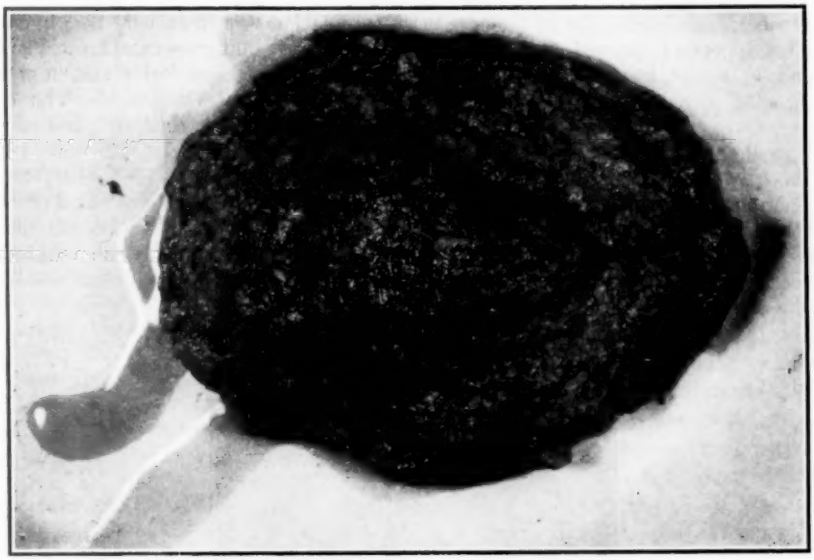

FIG. 4.—*Case 1.* Stool showing typical steatorrhea. Note oily liquid flowing freely about margin of stool.

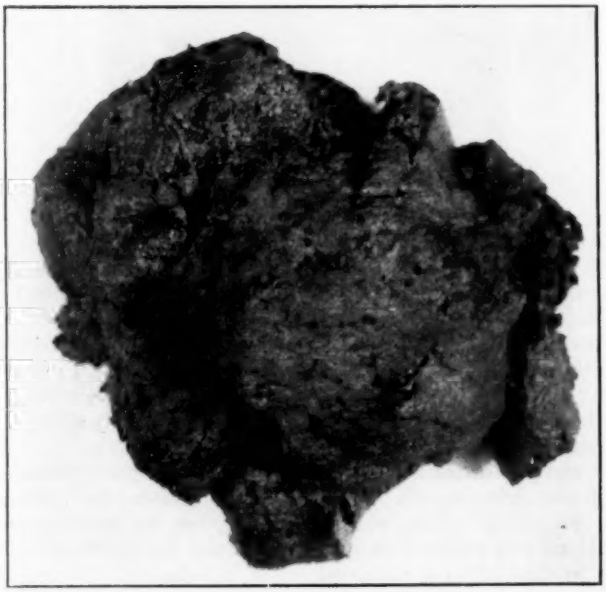

FIG. 5.—*Case 1.* Appearance of stool after two weeks' therapy.

that there was a substantial reduction of fat in the stool and an increase in the patient's weight.

On this regimen he made steady progress. The number of stools dropped from 11 or 12 to 1 or 2 daily. They remained bulky and formless but grossly they were free of excess fat and no longer fetid. He felt generally better, his appetite improved and he gained 13 pounds in weight, but was not completely free of mild attacks of abdominal pain. However, these attacks were distinctly less intense in character and of shorter duration than those he had previously experienced. The general improvement was sufficient to permit his discharge from the hospital and he was advised to return to the out-patient clinic for further follow-up.

FIG. 6.—*Case 2.* Roentgenogram showing extensive calcification of the pancreas.

The laboratory findings on this patient for all admissions are summarised in Table 1.

CASE 2. E. K., white, male, aged 47. Occupation, elevator operator. This patient was admitted to the hospital on August 13, 1943, complaining of right upper quadrant pain which had been recurring at irregular intervals over a period of nine years. It was colickly in nature and penetrated through to the back beneath the right scapula. With each recurrence the initial phase was so severe that morphine was required to give relief and he would then follow a restricted diet for a variable period of time until the pain disappeared. During one of these episodes he noticed that his skin was slightly yellow.

Except for the abdominal pain referred to above, the only relevant finding in his personal history was that he indulged heavily in alcohol. Upon admission the physical examination was essentially negative except for moderate tenderness and muscle guarding over the gallbladder region and in the right flank. No icterus was present. The temperature was 101.8 F. which dropped slowly to normal within 3 days.

Hemoglobin was 78%, erythrocytes 3,900,000 per cu. mm. The blood prothrombin time was 44% on August 4th and 82% on August 12th. The serum amylase was 88 units, and the plasma protein was 5.8 gm. On August 4th the qualitative van den Bergh reaction was negative direct and quantitative 1.3 mg. per 100 cc., and on August 12th there was still a negative direct reaction and serum bilirubin was 0.2 mg. The urea clearance was 73% of average normal. A routine urinalysis was negative except for 1-plus albumin.

A cholecystogram showed a normally functioning gallbladder without evidence of calculi, but the presence of extensive calcification of the pancreas was noted.

A Roentgen-ray picture of the chest revealed prominent hilar shadows in both lung

fields and minimal tuberculosis in the left second intercostal space.

The patient was given bed-rest and treated symptomatically; the pain subsided slowly over a period of 9 days and he was discharged symptom-free on August 19, 1943, with a diagnosis of acute cholecystitis which had subsided.

Since this patient was not re-admitted, an attempt was made to trace him through his former employer and we learned that he had died in June, 1945, in a Veterans' Tuberculosis Sanitarium. Unfortunately no autopsy was performed and there were no records available indicating that any further pancreatic dysfunction had been recognised. Nevertheless, on the basis of the long history of repeated attacks of severe abdominal pain, the transient mild jaundice and the presence of marked, diffuse calcification of the pancreas seen upon Roentgen-ray examination, we felt that this patient represented an additional case of disseminated calcification of the pancreas.

Comment and Conclusion. Probably one of the greatest benefits that will accrue from the proper recognition of this disease is that it may prevent the needless removal of a gallbladder, appendix or kidney. As has been demonstrated in one of our patients the erroneous removal of his gallbladder led to a series of operations to overcome the sequels of the first, without in the least benefiting the condition giving rise to the initial symptoms. On one occasion, due to the persistent complaint of abdominal pain for which no organic cause could be found, this patient was also diagnosed as a psychoneurotic. That this error has occurred previously is indicated by the paper of Yaskin[14] who reported 4 cases of pancreatic disease in 1931 in whom a diagnosis of functional disturbance was made, and by that of Rickles[9] who in 1945 added 3 cases with depression and anxiety as the presenting symptom. Both authors emphasize that the clinician should always be on guard to rule out disease of the pancreas when deep-seated pain in the epigastrium is associated with mental symptoms. Remaining alert to the possibility of the existence of disseminated calcification of the pancreas in a patient is probably the most important single factor in its recognition.

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EXPERIENCES WITH PENICILLIN AND DICUMAROL IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*

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Almost simultaneously in March, 1943, it was reported in both the United States[13] and England[11] that during treatment of subacute bacterial endocarditis with penicillin the blood was freed of green-producing streptococci, but that the infection recurred after the withdrawal of penicillin. This concept persisted throughout 1943. In January of 1944, Loewe and his associates[15] reported on 7 consecutive cases in which the use of penicillin and the simultaneous administration of the anticoagulant heparin had proved successful.

This was the status of our knowledge when penicillin became more readily available for civilian use in June of 1944. A few earlier attempts had been made at the State of Wisconsin General Hospital to treat subacute bacterial endocarditis with the new drug. Varying quantities of penicillin were used and the treatment was carried on for various periods of time. Because at that time an anticoagulant seemed to have definite value, it was decided to use Dicumarol in combination with penicillin. Dicumarol, 3,3[1] methylenebis (4-Hydroxycoumarin), had been identified by Professor K. P. Link and his associates[7,8,14,24] as the toxic factor in spoiled sweet clover and was later isolated and crystallized by them. It had been used clinically by Meyer et al.[2,19] and Allen et al.[6] as an anticoagulant. After having used heparin and the sulfonamides in the treatment of subacute bacterial endocarditis, Allen[1] at the Mayo Clinic substituted Dicumarol, but fatal cerebral hemorrhages occurred as they had with the former combination of heparin and sulfonamide. Experiences with our early cases have been reported in two previous papers[18,25].

One year after the report of Loewe, however, Dawson and Hunter[9] published their results with two series of cases, in the first of which they used a combination of penicillin and heparin and in the second penicillin alone. The results in the two series were equally favorable. The experience of Bloomfield[3] in California and of Katz[20] in Chicago also indicated that the anticoagulant was unnecessary. The reports which continue to appear in the literature[16,21,23] indicate that at least 50% or more of unselected cases are arrested.

There is a marked difference of opinion as to the optimum length of time that therapy should be continued. Bloomfield, et al.[3,4,5] lean toward prolonged therapy, a view which we share[18]. Meads, Harris and Finland[17], on the other hand, obtained comparable results with therapy of no more than 2 weeks' duration, and similar findings are reported by Hunter and Dawson[10] who found intensive courses over relatively short periods of time to be effective. The method of administration is also in question. Bloomfield and his group[4] lean toward interrupted intramuscular injections in the majority of cases, as we do also; Goerner and Blake[12] favor the continuous intravenous route, and Dawson and Hunter[10] feel that their best results are obtained by continuous intramuscular injections.

Methods. In general, pencillin was administered only to patients from whom at least 2 positive cultures had been obtained.

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The organism was checked in vitro to determine its sensitivity to penicillin, by a method similar to that of Thomas, Levine, and Vitagliano[26]; drops of various concentrations, namely, 0.05, 0.25 and 0.5 units per cc., were placed in small wells on an agar plate and the resulting zone of inhibition was noted. A suitable method for clinical administration was developed early. By the time 3 or 4 cases had been treated certain broad principles had been evolved. Six weeks was decided upon as the shortest period of time in which organization of vegetations could be expected and penicillin administration was carried on for at least that long. As penicillin was still relatively scarce, it was given intramuscularly in 6 daily doses for a total of 120,000 units. Later, with added experience, and more penicillin available, we concluded that this dosage should be increased, and treatment was started with an intramuscular injection of at least 25,000 units every 3 hours. Intramuscular administration being the most convenient, was utilized in all cases unless the patient did not respond and a trial by another route seemed indicated. In several refractory cases we later administered 1,000,000 to 3,000,000 units of penicillin daily by continuous intramuscular or intravenous drip. Dicumarol was administered in an initial dose of 4 or 5 mg. per kilogram. Subsequent daily doses of 1.5 mg. per kilogram were given to maintain a prothrombin time between 25 and 50% of normal, as determined by Pohle and Stewart's[22] modification of the Quick method. In the first trials Dicumarol was begun shortly after the initiation of penicillin therapy. After the death of a patient (Case No. 9) following a few days of combined therapy, possibly from cerebral hemorrhage, it was decided to begin Dicumarol therapy only after the temperature became 99 or less or after the cultures became negative. Penicillinase was not used in the culture media in this study, and this was probably responsible for suppression of many otherwise positive blood cultures. The patients were, however, kept in the hospital for 5 to 14 days after treatment was finished and cultures were taken every day or two during this time. The first check-up examination was usually advised at the end of one month, at which time most of the relapses were obvious.

Results. Thirteen cases were treated with penicillin and Dicumarol (Table 1). Of this group, 11 had rheumatic valvular lesions, 1 had a congenital lesion, and 1 was believed to have a combined congenital and rheumatic lesion. Seven recovered and remained well for intervals of 10 to 17 months. The duration of symptoms before therapy was begun ranged from 1 to 17 months, the average being $3\frac{1}{2}$ months. After therapy was initiated, fever usually subsided by the 14th day, the average being $12\frac{1}{2}$ days. In all but one case cultures became negative in 1 to 3 days; in that case it took 27 days. The average length of time that elapsed before negative cultures were obtained was $5\frac{2}{3}$ days. The smallest total dosage administered in these successful cases was 2,500,000 units and the largest 20,200,000. Only 2 of these patients had received penicillin therapy previously. The blood cultures of all were positive for *Streptococcus viridans*, and all of the organisms were sensitive to penicillin in vitro, giving inhibition with 0.05 unit per cc. We include the summary of one of these successful cases.

Case Reports. CASE 3. A 24-year-old white male entered the hospital on August 23, 1944. In May he had had "grippe" with chills, fever, and backache. Sulfonamide therapy gave temporary relief for approximately a week, after which the symptoms recurred. Past history revealed that at the age of 9 he had had rheumatic fever. Physical examination showed that the patient was acutely ill, and scattered petechiae were noted. The heart showed signs of a double aortic lesion. The spleen was barely palpable. There was mild anemia, and 3 cultures were positive for *Streptococcus viridans*, sensitive to penicillin, with a zone of inhibition of 25 mm. around a drop containing 0.05 unit per cc. On September 1, 1944, penicillin in quantities of 35,000 units every 4 hours injected intramuscularly was started along with Dicumarol. On September 16 penicillin was reduced to 25,000 units every 4 hours, on the 30th to 20,000 units, and on October 4th to 15,000 units. It was discontinued completely on October 12th. The initial fever in this case was 105.8 degrees F.

and by the second day of therapy it had decreased to 99. The first negative blood culture was obtained on September 2nd. The course was uneventful and he was discharged on October 19, 1944. A subsequent check-up in March of 1945 revealed that there had been no recurrence of symptoms, and 3 negative cultures were obtained. On March 29, 1946, there was still no evidence of recurrence.

Another patient (Case 8) had a relapse after almost a year, during 7 months of which he had been working. He had had a tooth extracted and had been given what was erroneously thought to be adequate prophylactic penicillin therapy. Penicillin was given 14 hours before and 54 hours after the extraction in quantities of 15,000 units every 3 hours. Within a week, however, he again had chills and fever, and positive cultures for *Streptococcus viridans* were obtained. He was under therapy from June, 1945, to February, 1946, but the condition was not arrested. He is being treated again and will be the subject of a separate report.

Of the 5 unsuccessful cases in this group, 3 relapsed promptly after the discontinuance of therapy. Two of these (Cases 11 and 13) had received previous penicillin therapy in inadequate doses and the third (Case 12) left the hospital against our advice before completing the minimum 6 weeks' course which we had advocated. These 3 have made recoveries on penicillin therapy alone in massive doses and case summary No. 11 follows.

Case 11. A 21-year-old white male had been a patient here in January of 1944. At that time a diagnosis of subacute bacterial endocarditis with rheumatic mitral stenosis and insufficiency had been made. Sulfamerazine and typhoid vaccine gave temporary improvement. He returned on May 23, 1944, and cultures were persistently positive for *Streptococcus viridans*. He had a gnawing abdominal pain, nausea, and hematemesis and was placed on a modified Sippy regimen. Subsequent studies of his gastro-intestinal

Table 1.—Cases Treated With Penicillin and Dicumarol

Case No.	Discharge Date	Age Yrs.	Duration of Symptoms	Organism	Previous Therapy	Penicillin Units Total Dosage	Fever to	Days After Rx.—99°	First Negative Culture after Rx.	Course
Case 1 N.E.W.	8-30-44	38	6 mo.	Strep. viridans	0	2,500,000	102[2]	1 day	1 day	Arrested.
Case 2 J.G.W.	8-31-44	40	2 mo.	Strep. viridans	0	3,185,000	104[1]	14 days	2 days	Arrested.
Case 3 R.M.	10-19-44	24	3 mo.	Strep. viridans	0	6,300,000	105[8]	1 day	1 day	Arrested.
Case 4 G.W.	12-19-44	39	4 mo.	Strep. viridans	+	6,000,000	101[2]	19 days	2 days	Arrested.
Case 5 F.K.	3-5-45	33	4 mo.	Strep. viridans	+	20,200,000	102	36 days	2 days	Arrested.
Case 6 B.R.	3-20-45	48	3 mo.	Strep. viridans	0	8,535,000	102[2]	12 days	27 days	Arrested.
Case 7 D.K.	3-31-45	16	1 mo.	Strep. viridans	0	7,095,000	101	2 days	3 days	Arrested.
Case 8 J.R.	8-19-44	48	5 mo.	Strep. viridans	0	4,295,000	103	6 days	4 days	Relapse. 1 yr. after dental extraction.
Case 9 G.W.	10-12-44	33	7 mo.	Strep. viridans	+	720,000	103[2]	Never	Never	Died — Possible cerebral hemorrhage.
Case 10 D.D.	2-7-45	40	7 mo.	Strep. viridans	+	12,805,000	101[6]	Never	Never	Died.
Case 11 L.M.W.	2-7-45	21	17 mo.	Strep. viridans	+	23,760,000	101	7 days	Never	Arrested after 42,000,000 intensive.
Case 12 R.J.S.	7-5-45	22	2 mo.	Strep. viridans	0	4,960,000 6,385,000	103	6 days	2 days	Arrested after 52,914,000 intensive.
Case 13 J.F.S.	8-27-45	39	6 mo.	Non-hemo. strep.	+	8,360,000	100[4]	2 days	41 days	Arrested after 20,840,000 intensive.

tract, including Roentgen-ray, esophogoscopy, and gastroscopy, failed to reveal the source of this trouble. Penicillin became available at this time and he was given 1,100,000 units, starting June 27, 1944, and after 1 week on this therapy his temperature was normal and the cultures were negative. He was discharged on July 10, 1944. When he returned on October 2, 1944, the blood cultures were again positive, and combined therapy, 25,000 units of penicillin every 4 hours intramuscularly and oral Dicumarol, was instituted. This was gradually reduced and toward the end of a course of 11,860,000 units, 5 negative blood cultures were obtained. He was discharged on December 20, 1944. He was admitted once more on February 7, 1945, when cultures were again positive. Penicillin was given in quantities of 50,000 units every 3 hours for a total of 23,760,000 units along with Dicumarol. The temperature, which had been 101 on admission, fell to normal a week after therapy was begun. On March 28, 1945, he had another hematemesis, and at this time Dicumarol was stopped. Again diagnostic studies were negative. He recovered rapidly from this episode and was discharged at his request on June 5, 1945. All cultures during this stay were positive. On July 10, 1945, after having another hematemesis, the patient returned. He was now given 1,000,000 units of penicillin daily in 1,000 cc. of glucose as a continuous intravenous drip. No Dicumarol was given. The therapy was continued for 42 days. Only 1 culture (on August 10, 1945) was positive. He was discharged on August 24. When seen in check-ups on September 26 and November 27, 1945, and on March 26, 1946, he was getting along well, and the 9 cultures taken at these times were negative.

The 2 cases which were complete failures include a 40-year-old white female (Case 10), with a *Streptococcus viridans* organism sensitive to penicillin in quantities of 0.25 unit per cc., who was under therapy for almost 4 months. She had previously received 2 short courses of penicillin elsewhere consisting of 2,500,000 units and 3,000,000 units respectively, each of which given over a 10-day period resulted in temporary relief of symptoms. She received penicillin here in quantities as high as 25,000 units every 2 hours, intramuscularly, and for a time part of the daily dosage was given by the continuous intravenous route. A total of 12,805,000 units was given. During her entire stay she ran a septic type of fever, and cultures were persistently positive. The last case (Case 9) had a *Streptococcus viridans* organism which was resistant to the action of penicillin, and she apparently died of a cerebral hemorrhage following initiation of the combined therapy, though autopsy was not permitted.

Nine patients received penicillin alone, 8 of whom had rheumatic lesions and 1 a possible combined congenital intraventricular septal defect and rheumatic mitral and aortic disease (Table 2). Two of these were in the group before our organized plan was established. In others Dicumarol was withheld because negative blood culture and control of fever were not obtained. Two others are in the group because anticoagulant therapy seemed contraindicated. Of the total group of nine, 4 died and came to autopsy, and the following findings were noted. The first (Case 17) was a 76-year-old white male who received 15,000 units of penicillin every 4 hours intramuscularly for a total of 810,000 units. At autopsy an ulcerated vegetation was noted on the mitral valve, which showed previous rheumatic damage. There were many bacterial colonies and no evidence that the vegetation was healing. Splenic infarctions were also present. The second (Case 18) was a 46-year-old white male who had previously received inadequate therapy. He was given 3,420,000 units in approximately 11 days in quantities as high as 50,000 units every 3 hours, intramuscularly. He developed a pulmonary infarction and died. Autopsy revealed that the aortic valve was involved, and though it was obvious that repair had proceeded, with fibroblastic activity and some calcification, this did not counterbalance the destructive process and a few "puny" colonies were seen. The third case (Case 19) was the first patient to receive penicillin for subacute

bacterial endocarditis at this hospital. He was 51 years old and had had a total of 2,000,000 units intramuscularly, 15,000 units every 4 hours, for 22 days; and at the time of his discharge from this hospital, cultures were negative. Approximately 5 months later he developed congestive heart failure and died at another hospital. At that time cultures were negative. Autopsy showed organized lesions on the valves, but scattered colonies of bacteria were present in the organized tissue. The last case (Case 20) is described in some detail because of the findings on the heart valve when autopsy was performed.

TABLE 2.— CASES TREATED WITH PENICILLIN

Case No.	Discharge Date	Age Yrs.	Duration of Symptoms	Organism	Previous Therapy	Penicillin Units Total Dosage	Fever to	Days After Rx.—99°	First Negative Culture after Rx.	Course
Case 14 C.L.P.	7-1-44	13	1 mo.	Type V Pneumo.	0	2,160,000	105[4]	18 days	2 days	Arrested.
Case 15 S.G.	11-4-44	33	7 mo.	Strep. viridans	0	5,860,000	102	2 days	2 days	Arrested.
Case 16 V.A.K.	12-5-45	31	2 mo.	Strep. viridans	+	26,475,000	102[4]	2 days	17 days	Arrested.
Case 17 P.D.L.	6-22-44	76	½ mo.	Strep. viridans	0	810,000	105	Never	Never	Died.
Case 18 E.S.	7-23-45	46	4 mo.	Strep. viridans	0	3,420,000	104[8]	Never	9 days	Died.
Case 19 J.I.	7-11-44	51	11 mo.	Strep. viridans	0	2,000,000	103[2]	13 days	1 day	Died — Congestive heart failure.
Case 20 J.A.K.	11-8-44	30	2 mo.	Non-hemo. strep.	0	1,250,000	103[4]	Never	1 day	Died — Congestive failure & complications.
Case 21 J.H.N.	1-20-45	39	1 mo.	Strep. viridans	+	180,000	102[2]	1 day	Never	Died.
Case 22 G.K.	6-29-45	20	5 mo.	Strep. viridans	+	31,900,000	103	Never	Never	Died.

CASE 20. A 30-year-old white female entered the hospital on September 19, 1944, as an emergency case; she had severe pain in the right upper quadrant, abdominal distention, nausea, vomiting, chills, and fever. Symptoms had begun 5 weeks previously, had become progressively more severe; during this time there had been a 25-pound loss of weight. She had had similar complaints prior to a cholecystectomy in 1935. On physical examination she appeared pale and acutely ill; respirations were rapid and shallow and the fever was 101. There were a few basal râles in the right lung, the right diaphragm was elevated and there was no excursion. The heart was enlarged, systolic aortic and mitral murmurs were noted. There was abdominal distention, tympany, and marked tenderness, especially in the right upper quadrant with muscle spasm and rebound tenderness. The liver was 4 cm. below the right costal margin. Laboratory studies showed a hemoglobin of 8 grams, red blood cell count of 2,860,000, white blood cell count of 11,200 with 90% neutrophils. A urinalysis showed 0.07% albumin with clumps of white blood cells. A fluoroscopic examination substantiated the fact that the right leaf of the diaphragm was not moving. The impression was subphrenic abscess and bilateral pyelonephritis, and after several transfusions a surgical exploration for possible drainage of the subphrenic abscess was made. About 500 to 800 cc. of clear yellow fluid were removed, and a liver biopsy showed subacute to chronic hepatitis. A cystoscopic examination later confirmed the diagnosis of pyelonephritis on the right due to *B. Aerogenes* and on the left due to *Streptococcus fecalis* and *B. Pyocyaneus*. While in the hospital her course continued to be stormy; she developed petechiae and after several negative blood cultures one was obtained which was positive for a nonhemolytic streptococcus. Sulfadiazine had been of no avail and with the positive culture a tentative diagnosis of

subacute bacterial endocarditis or periarteritis nodosa was made and penicillin was given, 15,000 units every 4 hours for a total of 1,250,000 units. In spite of this therapy, nausea and vomiting became marked and the patient died on November 18, 1944. An autopsy was performed, which showed subacute bacterial endocarditis with small vegetations on the aortic and mitral leaflets, splenic infarctions with rupture of one into the subphrenic space, renal and liver infarction, rheumatic endocarditis, chronic pericarditis and myocardial infarction. Besides this, periarteritis nodosa was present. The description of the valve is worthy of note. The aortic leaflet showed a small vegetation 0.5 mm. in diameter. The mitral leaflet had one small adherent vegetative area 2 mm. in diameter. On microscopic examination there was hyalinization of the vegetations which were completely sterile. The subacute bacterial endocarditis appeared to be healed.

Three of the cases described above had fairly large lesions. The finding of colonies on an organized valve, as in Case 19, has been previously reported by Bloomfield[4]. The complete healing of Case 20 is of interest. This might have occurred without therapy in the natural course of the disease. On the other hand, since the vegetations were small, therapy may have been adequate in this case.

Of the remaining cases which did not receive Dicumarol, one, a 33-year-old white female, was 5 months pregnant and stated at the time of admission that she had vaginal bleeding. She also had jaundice thought to be due to cholecystitis and cholelithiasis. She responded to penicillin therapy alone. Two other patients did not receive Dicumarol, one because the prothrombin time was low on admission (Case 14, a *Type V Pneumococcus* infection) and the other (Case 16 with a *Streptococcus viridans organism* present) because he had had a stormy course before therapy was started. The 2 remaining cases have died, one in the hospital of a convulsion after receiving only 160,000 units, the other at home, her symptoms never having come under control in spite of 31,900,000 units, part of which dosage was administered in combination with sulfadiazine for 7 days, and part of it by the constant intravenous drip.

Hence, in the entire group of 13 cases that received the combined therapy, 8 were arrested, 1 of these relapsed after a year, 3 additional cases recovered on later regimens of intensive penicillin therapy alone. Of 9 treated with penicillin alone, 4 were arrested, 1 of these died and sterile healed vegetations were noted at autopsy, and another with negative cultures 5 months after therapy showed colonies still present in the vegetation at autopsy. Fifteen absolute arrests were obtained in the total series of 22 cases.

We noted that the early cases in our series were easily controlled, whereas later we encountered more that were refractory and there was difficulty in getting the patients under control. We got the impression that this occurred after penicillin became more readily available for civilian use and that a larger number of cases had been subjected to inadequate therapy before coming under our observation. We therefore analyzed our cases as to previous penicillin therapy during the course of the illness (Table 3). Ten of the patients had received previous penicillin therapy, a number of them in large doses for a short period of time. One other had undergone an interrupted course of therapy. All but one of these had improved temporarily with the initial therapy received elsewhere. Of this group 3 died before completion of our therapy and 2 other cases never came under control. Of the remaining 6, one had a drop in temperature in 2 days and a negative culture on 30,000 units every 3 hours, and one became normal in 3 days on 40,000 units every 3 hours, a third on 1,000,000 units daily in 8 days. But the others had fever for 20 to 28 days and the average period of fever for the group was $16\frac{1}{6}$ days, as compared with $8\frac{1}{3}$ days for those who had received no previous therapy. In cases previously untreated, cultures became negative on an average of $4\frac{2}{3}$ days after initiation of therapy, as

compared with 11½ days in cases that had had previous therapy. A conclusion as to the significance of this point is not justified, but it may be highly significant. No explanation has presented itself, since in all but one of these cases the organism was still sensitive in vitro.

In this group of 22 cases, 13 had petechiae on entrance to the hospital. In only 2 of these did petechiae persist throughout treatment, despite freedom from fever and negative blood cultures. In these 2 cases, cultures became positive 1 or 2 weeks after the discontinuance of therapy. When the patients were later subjected to regimens that were to prove effective, embolic phenomena did not occur.

Comment. It is difficult from this series to decide upon an optimum dosage of penicillin. When we started the study, the quantities utilized obviously gave adequate blood levels for only a short time, yet these cases included our greatest number of successes. On the whole the organisms were rather sensitive to penicillin, and it seemed that adequate levels for 1 hour out of 3 or 4 was sufficient. This follows closely the findings of Bloomfield and Halpern[5], who were able to control 3 of 4 cases treated with 4 injections daily of 50,000 units each. We agree with these authors that very large doses are probably unnecessary in the ordinary case. In our Cases 11, 12 and 13, however, which were refractory, intensive therapy undoubtedly was responsible for their arrest.

The difference in favor of combined penicillin and Dicumarol therapy is not as significant as it would seem, since after the first 4 cases only those that were responsive to penicillin received Dicumarol. It is especially significant that 3 of the most refractory cases which did not respond to doses of 8,360,000 units, 23,760,000 units and 11,345,000 units of penicillin respectively when it was combined with Dicumarol did later respond to total doses of 20,840,000 units, 42,000,000 units and 52,940,000 units administered without Dicumarol. We are, therefore, decidedly skeptical that any benefits are to be derived from anticoagulant therapy, which certainly carries with it grave hazards in subacute bacterial endocarditis. Penicillin therapy, however, has given decidedly better results than anything previously available.

The need for sensitivity tests was apparent from the start, and there was good correlation between sensitivity of the organisms and clinical response. In the early cases the levels of penicillin in the blood were not obtained because of the lack of technical aid. In our recent cases, however, we have been making these determinations, and they are of definite value in regulating the dosage, especially in the refractory cases. There is no clear cut

Table 3.—Comparison of Cases With and Without Previous Penicillin Therapy

NO PREVIOUS THERAPY				PREVIOUS THERAPY			
Case No.	Total Dosage Units	Days After Rx.—99°	First Negative Culture	Case No.	Total Dosage Units	Days After Rx.—99°	First Negative Culture
1	2,500,000	1 day	1 day	4	6,000,000	19 days	2 days
2	3,185,000	14 days	2 days	5	20,200,000	36 days	2 days
3	6,300,000	1 day	1 day	11	42,000,000	18 days	29 days
6	8,535,000	12 days	27 days	13	20,840,000	3 days	2 days
7	7,095,000	2 days	3 days	12	52,914,000	2 days	20 days
8	4,295,000	6 days	4 days	16	26,475,000	28 days	17 days
14	2,160,000	18 days	2 days				
19	2,000,000	13 days	1 day				
15	5,860,000	2 days	2 days				
Average	4,658,888	7⅖ days	4⅖ days		28,071,366	17⅖ days	12 days
Patients who died before therapy was completed							
17	810,000			9	720,000		
20	1,250,000			21	180,000		
				10	12,805,000		
				22	31,900,000		
				18	3,420,000		

evidence that it was more difficult to treat patients with long-standing symptoms than those with more recent symptoms. It is probable, however, that the size of the vegetation as well as the extent of destruction to the heart valve contributes to the refractory nature of some cases. Case 20, if she had active lesions at the time first seen, emphasizes this point. The presence of colonies of organisms in the valve in Case 19 likewise brings up a point previously noted by Bloomfield[4]. This may later be the source of a recurrence, or hyalinization and calcification may become so complete that the focus is walled off.

Summary and Conclusions. Of 22 patients with subacute bacterial endocarditis, 13 received both penicillin and Dicumarol, and 9 were given only penicillin. From our experience to date, we have acquired certain impressions and tentative conclusions:

1. Treatment with penicillin alone or where combined with Dicumarol should be persistent for a minimum of 6 weeks.

2. This prolonged therapy has given decidedly better results than anything previously employed.

3. Despite our results favoring combined therapy, we remain decidedly skeptical that anticoagulant therapy offers any advantages and it is unquestionable that anticoagulant therapy carries with it grave hazards in subacute bacterial endocarditis.

4. Penicillin therapy for 54 hours after removal of a focus of infection is *inadequate* to prevent the development of subacute bacterial endocarditis.

5. It was noted that patients who had received distinctly inadequate therapy before coming under observation presented a more difficult problem as far as control was concerned. Five of 7 failures were in this group. All but 1 of the inadequately treated patients had become subjectively and objectively improved under the original penicillin therapy. We raise the question as to the possible great significance of this point and although a final conclusion regarding it is not justified, it may be important.

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THE TREATMENT OF ACUTE DIPHTHERIA AND THE CHRONIC CARRIER STATE WITH PENICILLIN*†

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Since the introduction of antitoxin by Behring,[3] no other agent capable of exerting a specific effect in infections due to *Corynebacterium diphtheriae* has been discovered. The modern treatment of diphtheria, therefore, is directed entirely towards neutralization of circulating toxin. The causative organisms are not affected primarily by the method of treatment in use and are eradicated from the focus of infection mainly through the activity of the normal tissue defense mechanisms.

The sulfonamides have been found to exert little effect against the organism of diphtheria. Examination of the *in vitro* susceptibility of *C. diphtheriae* to penicillin by Fleming,[6,7] Chain et al.,[5] Abraham et al.,[1] and by Herrell[10] have shown that this bacterium is susceptible to the antibiotic agent. Heilman[9] established fatal infections in both guinea pigs and hamsters with the gravis strains of *C. diphtheriae* and administered penicillin in quantities usually effective against the organisms but failed to protect either of these experimental animals against the infection. Four cases of nasal and faucial Klebs-Loeffler bacillus infection were treated by Turner[15] with nasal drops containing 250 units of penicillin per cc., given every 3 hours for 48 hours, with the resultant clearing of the organism from the mucous membrane in 24 hours.

Twelve patients who had diphtheria due to the gravis strain were treated by McSweeney[12] with both intramuscular injections and throat and nasal spray of penicillin in doses of 202,500 to 750,000 units. Four of the individuals died. The antibiotic agent was thought to produce more rapid subsidence of the faucial edema and "bull neck" and to hasten clearing of the diphtheritic membrane. Nose and throat cultures did not reveal *C. diphtheriae* as long as penicillin spray and nose drops were used. The author concluded that between 700,000 and 800,000 units of penicillin were necessary in the treatment of Grade 3 and 4 diphtheria.

In spite of the fact that a large number of different agents and procedures have been examined for their effect on the carrier state in diphtheria, very little progress has been made in the development of an efficient method for eradication of *C. diphtheriae* from the noses and throats of healthy individuals who harbor them. Very little work has been done on the treatment of diphtheria carriers with penicillin, and only 4 reports have been found in the literature on this subject. Large amounts of penicillin were administered intramuscularly to diphtheria carriers from 1 to 2 weeks by Peterson, Northrop, and Herrell.[14] In a few cases, negative cultures were obtained at the time the antibiotic agent was administered or shortly after therapy had been completed. "However, there were recurrences." Berman and Spitz[4] treated 10 proven diphtheria carriers by the instillation of 1 cc. of solution containing 500 units of penicillin 4 times each day for 5 days, and immediately after each nasal instillation,

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spraying the fauces and the posterior wall of the pharynx with 1 cc. of the same solution. They reported a reversion to a non-carrier state within a period of 5 days. Eight of the cases were followed for 4 weeks and were found to remain free of the Klebs-Loeffler bacilli.

Treatment with 300,000 units of penicillin per day by the intramuscular route was reported by Kocher and Siemsen[11] to be without influence on the diphtheria carrier state. When lozenges containing 500–1,000 units of the antibiotic agent were administered to patients hourly for 12 doses over a period of 3 to 15 days, and, in addition, nasal sprays of the drug were given every 2 hours, 74% of the cases showed eradication of the diphtheria bacilli from the nose and throat. Tonsillectomy produced clearing of the organisms in those individuals in whom no results were obtained with penicillin lozenges and sprays. Paull, Tucker, Holladay, and Nicewonger[13] were unable to show any effect on the diphthetia carrier state by penicillin in the nebulized state.

The purpose of the work reported here was to examine the effect of penicillin on the clinical course and bacterial flora of the nose and throat in acute cases of diphtheria, and to determine the value of the drug in the chronic diphtheria carrier state.

Methods. All patients admitted to the hospital with a diagnosis of acute diphtheria or of the carrier state were subjected to a complete physical examination in which special attention was paid to the characteristics of any membrane present in the nose or pharynx. Cultures of both the nasal and pharyngeal mucosa, carried out immediately after entry to the hospital and daily thereafter until the patient was discharged from the hospital, were inoculated on heart-infusion-tryptose-yeast-blood-agar and tellurite agar. After incubation for 24 to 48 hours at 37° C., all suspicious colonies were stained with either Mallory's acid methylene-blue, or Loeffler's alkaline-methylene-blue and examined microscopically. In addition, all of the strains isolated were typed either in our own laboratories or in those of Dr. Howard Mueller of the Department of Bacteriology of the Harvard Medical School. Three times a week, cultures of the pharynx and nose were sent to the Massachusetts State Department of Health for confirmation. All strains of *C. diphtheriae* isolated from carriers were examined for virulence, and no case from which virulent organisms were not recovered was treated.

Penicillin was administered intramuscularly in a dose of 15,000 to 30,000 units every 3 hours for an average of 12 days after the diagnosis of acute diphtheria or the carrier state had been established bacteriologically; in about one-third of the cases, larger amounts of the drug were given. All of the patients with acute infection received an adequate quantity of diphtheria antitoxin. Electrocardiograms were taken frequently and physical examination of the heart and nervous system carried out daily in order to detect the onset of myocarditis or polyneuritis. All patients were followed clinically and bacteriologically for a minimum of 2 weeks after penicillin treatment had been stopped; in some cases, the follow-up period was as long as 2 months.

Results. I. *Cases of Acute Diphtheria.* Thirty-eight cases of diphtheria involving various portions of the upper respiratory tract were treated with antitoxin alone or with antitoxin plus penicillin.

Twelve patients were given only diphtheria antitoxin. Their ages ranged from 5 to 43 years (average, 18.5), and they had been ill with signs and symptoms of diphtheria for from 2 to 8 days before admission to the hospital. In 8 of the individuals, the disease was confined to the pharynx, in 1 it involved both the nose and pharynx, in 1 the pharynx and larynx, and in 2 was limited to the nasal mucous membrane. All of the patients were found to be infected with the mitis strain of *C. diphtheriae* and were given between 5,000 and 60,000 units of diphtheria antitoxin intramuscularly and/or

intravenously. Eleven had an uncomplicated clinical course and 1 developed acute myocarditis. Studies of the time required for the diphtheria organisms to disappear from the nose and pharynx revealed that in one instance *C. diphtheriae* was not recoverable 5 days after antitoxin had been given. In the other 11 cases, between 17 and 75 days were required for eradication of the Klebs-Loeffler organism; in 2 individuals, the organisms disappeared after 18 days, and in 2 after 30 days. In 1 instance each, the Corynebacteria could be recovered up to the 10th, 17th, 25th, 47th, 51st, 73rd, and 75th days after antitoxin treatment. The average time required for disappearance of *C. diphtheriae* in this group of patients was 33.25 days.

Twenty-six cases of acute diphtheria were treated with penicillin in addition to antitoxin. The ages of the individuals in this group varied between 2 and 65 years (average, 21.4) and they had been ill for 2 to 11 days (average, 4.75 days) before admission to the hospital. Distribution of the diphtheritic lesions was as follows: In 21, the pharynx alone was involved, in 2 the pharynx and nose, in 1 the pharynx and larynx, and in 2 the pharynx, larynx, and nose. These patients were all infected with the mitis strain of *C. diphtheriae* and received between 20,000 and 80,000 units of antitoxin by the intramuscular and/or intravenous route (average, 32,000 units); in addition, they were given varying amounts of penicillin. The first three cases were treated with 120,000 units of penicillin per day for slightly less than 3 days (total, 330,000 units). When this quantity was found to be ineffective, the dose was increased to 120,000 to 240,000 units a day for approximately 12 days. Two individuals in this group suffered from complications of diphtheria; one, who had received only 330,000 units of the drug, had severe myocarditis with heart failure and peripheral neuritis. Another, who had been given larger quantities of penicillin, developed polyneuritis with strabismus in the second week of his illness and weakness of all the extremities and complete areflexia 4 weeks later.

From 60 to 70 days were required before the cultures of the throat and pharynx became negative for *C. diphtheriae* in the 3 patients who received only 330,000 units of penicillin. In the 23 individuals given the larger doses of the antibiotic agent, the diphtheria bacillus disappeared from the nose and throat of 9 in 3 days, of 5 in 4 days, of 2 in 5 days, of 3 in 1 day, and of 1 patient each in 2, 7, 8, and 14 days, respectively. Negative cultures were obtained in 17 of the 23 cases (73.8%) in 4 days or less. The average time required for this group to become free of the Klebs-Loeffler bacillus was 3.96 days when the 3 cases receiving the smaller dose of penicillin were omitted from the calculation.

In order to conserve space, the individual histories and detailed data of each case have been omitted and the results summarized in Table 1.

II. *Diphtheria Carriers.* Ten individuals, ranging in age from 2 to 44 years, who had been proven carriers of virulent diphtheria bacilli for varying periods of time and were sent to the hospital because of board of health regulations requiring their quarantine, received no treatment after admission. Cultures of the nose and pharynx taken at frequent intervals revealed a very slow rate of disappearance of the organisms from these 2 sites. In 5 patients, *C. diphtheriae* persisted for 19, 38, 43, 49, and 52 days, respectively. Two cases were allowed to leave the hospital 54 days after admission, at which time they still harbored the Klebs-Loeffler bacteria. Two children who were siblings of a case of acute pharyngeal and laryngeal diphtheria were subjected to tonsillectomy and adenoidectomy 90 days after they had been discovered to be diphtheria carriers; 1 week after operation, nose and throat cultures were still positive.

Thirteen chronic carriers of *C. diphtheriae*, ranging in age from 3 to 40 years, were treated with penicillin. The first 2 individuals studied received only small

amounts of the drug, but thereafter, the total quantity administered was increased to 1,000,000 units or more. When 120,000 units of the antibiotic agent were given every day for 12 days (total, 1,440,000 units), the time required for the Klebs-Loeffler bacilli to disappear was between 3 and 30 days, but over 50% of the patients retained the organisms for fairly long periods of time. Since this amount of penicillin appeared to produce only slow clearing of the carrier state, the quantity of the drug was increased to 240,000 units per day for 12 days. The administration of the larger dose resulted in the eradication of *C. diphtheriae* in 3 to 4 days.

Two carriers, 1 of whom had received 1,440,000 units of penicillin in 12 days, another 2,760,000 units in 23 days, remained positive for 45 and 35 days, respectively. The first patient was retreated with 3,120,000 units in 12 days and showed complete eradication of *C. diphtheriae* from the pharynx and nose in 3 days. The second individual was given the same quantity of penicillin as in the first course of treatment but this was injected over a period of only 9 days instead of the original 23 days. With this treatment, the organisms disappeared in 2 days and could not be demonstrated at any time in the following 2 weeks.

All of the patients were followed clinically and bacteriologically at frequent intervals for a period varying from 8 to 45 days after penicillin treatment was stopped, the cultures being examined in 2 laboratories simultaneously.

The results of treatment of diphtheria carriers with penicillin are presented in Table 2.

Discussion. No striking alteration could be detected in the clinical course of cases of acute diphtheria which received penicillin in addition to antitoxin when compared with those given antitoxin alone. The outstanding difference between the 2 groups was a marked reduction in the time required for the causative organism to disappear from the pharynx and nose in those treated with penicillin. Although the number of patients studied was too small to draw any conclusions concerning the effect of penicillin therapy on the incidence of complications, the drug seemed to be of little value in this respect.

The time required for *C. diphtheriae* to be eradicated from patients who were treated with antitoxin alone varied between 17 and 75 days (average, 33.25 days), while in those treated with peni-

TABLE 1.—SUMMARY OF RESULTS OBTAINED IN THE TREATMENT OF DIPHTHERIA WITH PENICILLIN

	Type of Treatment	
Number of Cases	Antitoxin—No Penicillin 12	Antitoxin Plus Penicillin 26
Age	5–43 years (Average—18.5 yrs.)	2–65 years (Average—21.5 yrs.)
Locations of Diphtheritic Lesion	Pharynx, 8 Pharynx and Nose, 1 Pharynx and Larynx, 1 Nose, 2	Pharynx, 21 Pharynx and Nose, 2 Pharynx and Larynx, 1 Pharynx, Larynx and Nose, 2
Type of C. diphtheriae	All cases—mitis type	All cases—mitis type
Dose of Antitoxin (units)	5,000—60,000 (Average, 40,000)	20,000–80,000 (Average, 31,350)
Amount of Penicillin given during entire course of treatment (units)	0	3 cases—330,000 23 cases—1,440,000–2,290,000
Complications	Myocarditis—1 case	Myocarditis and polyneuritis—1 case Polyneuritis—1 case
Time required for disappearance of C. diphtheriae from nose and pharynx	17–75 days (Average—33.25 days)	3 cases receiving 330,000 Units of Penicillin—60–70 days (Average—66.6 days) 23 cases—1–14 days (Average—3.96 days)

cillin, excluding those receiving less than 1,000,000 units, it ranged between 1 and 14 days (average, 3.96 days).

The question may be raised as to whether 3.96 days may not be within the normal time necessary for clearance of diphtheria bacilli from infected individuals treated with antitoxin alone and that thought that the rate at which convalescent carriers ceased to harbor organisms was a direct function of the number of surviving positive carriers at any time, and that the disappearance of the bacilli from the pharynx followed the following simple logarithmic law: $\frac{\log n_1 - \log n_2}{t_2 - t_1} = k$,

TABLE 2.—SUMMARY OF RESULTS OBTAINED IN THE TREATMENT OF DIPHTHERIA CARRIERS WITH PENICILLIN

Name	Age	Penicillin No. of Days Given	Total Dose-Units	Time Required for C. diphtheriae to Disappear from Nose and Pharynx (days)	Follow-Up Period (days)
J. V.	23	7	540,000	9	10
W. S.	8	3	240,000	11	8
L. M.	2	13	1,240,000	13	14
B. K.	30	14	1,300,000	12	16
H. F.	9	13	1,440,000	30	14
V. M.	3	14	1,680,000	21	30
L. L.	40	9	1,080,000	3	21
M. W.	22	12	1,440,000	3	21
V. M.	13	12	1,440,000	5	21
C. L.	10	12	2,880,000	4	21
D. G.—First Treatment	20	23	2,760,000	23*	12
D. G.—Second Treatment	20	9	2,840,000	2	14
J. Q.—First Treatment	12	12	1,440,000	12†	45
J. Q.—Second Treatment	12	12	3,120,000	3	21
A. A.	16	12	3,120,000	2	14

* Cultures became negative in 23 days and then became positive again.
† Cultures became negative in 12 days and then became positive again.

the average of 33.25 days observed in those not receiving penicillin was unusual. A review of the literature on this subject reveals that the data obtained with reference to the time of disappearance of *C. diphtheriae* in individuals treated with penicillin are probably significant. Andrewes, Bulloch et al[2] state that, in general, a large number of cases of diphtheria lose the bacilli within a "few days" of the disappearance of the membrane and that the remainder gradually develop negative cultures; abnormal cases, however, may persist as carriers for many months. A careful study of the persistence of the causative organism in 450 cases of diphtheria was made by Hartley and Martin[8] who found that about 75% of the patients still harbored the bacteria 7 days after admission to the hospital, 67% showed positive cultures after 10 days, 50% after 14 days, and 30% after 21 days. It was

where n_1 and n_2 equal the number of individuals still carrying the organism at times t_1 and t_2. The results obtained indicated that about 5% of the surviving positive convalescents became negative each day.

Weaver[16] made a similar study of 500 cases and found that about 93% still carried *C. diphtheriae* at the end of 7 days, 72% after 14 days, and 43% after 21 days. He concluded that there was approximately a 9% decrease in the carrier rate each day.

A study of the rate of disappearance of the Klebs-Loeffler bacillus from the nose and pharynx of patients with acute diphtheria was made by Wright,[17] who analyzed his data on the basis of type of organisms producing the disease. Of individuals infected with the mitis strains, 56% were still positive after 7 days, 44% after 14 days, 36% after 21 days, 27% after 28

days, and then gradually decreasing numbers so that after 70 days, 4% still harbored the bacteria.

When the figures reported by Wright[17] are averaged, it is found that about 19.3 days was the mean time required for *C. diphtheriae* to disappear from the pharynx and nose. An analysis of 130 cases of diphtheria admitted to the Haynes Memorial Hospital over a period of several years and treated only with antitoxin revealed that an average of 19.1 days elapsed before the organisms disappeared. Although the value, 33.25 days, observed in the present study, is somewhat high as compared with the data present in the literature, this may be so because of the small number of cases analyzed. It seems very probable, however, on the basis of the findings of the present study as well as those that have been published in the literature with respect to patients treated with antitoxin alone, that the percentage of individuals free of diphtheria bacilli within 4 days after becoming ill is very low. The average time of 3.96 days for clearance of *C. diphtheriae* from patients treated with antitoxin and penicillin appears to be very significant, therefore, and seems to make tenable the conclusion that treatment with penicillin is very effective in shortening the carrier state in the acute stage of diphtheria.

The investigations reported here did not confirm the reports in the literature that the chronic diphtheria carrier state persists for only about 10 days, or Weaver's observation that about 40% of carriers become negative after 7 days, 65% after 20 days, and 87% after 40 days. A fairly large number of patients who were carriers of *C. diphtheriae* for periods ranging between 4 and 5 months were observed in the present study; in several instances, tonsillectomy did not result in eradication of the organisms. In view of these observations, the results obtained with penicillin in the elimination of the chronic diphtheria carrier state in 3 to 5 days appear very significant. and this type of treatment is worthy of further trial. The evidence obtained seems to indicate that a dosage schedule of 30,000 units of penicillin intramuscularly every 3 hours for 12 days is the most effective in the treatment of permanent diphtheria carriers.

The value of penicillin in the therapy of diphtheria appears to be its ability to shorten markedly the duration of the convalescent carrier state. There is no indication that penicillin has any beneficial effect on the clinical course of the disease, and its use does not eliminate the necessity of giving adequate quantities of antitoxin. The chronic diphtheria carrier state may be cured if adequate amounts of penicillin are administered parenterally.

Conclusions. 1. Penicillin has no effect on the clinical course of diphtheria, and its use in this disease does not eliminate the necessity of administering adequate amounts of antitoxin.

2. Penicillin reduces markedly the duration of both the convalescent and chronic diphtheria carrier states if given in sufficiently large quantities.

3. A dose of at least 120,000 and preferably 240,000 units of penicillin per day for 12 days is recommended for the treatment of acute diphtheria.

4. A minimum of 240,000 units of penicillin per day for 12 days is suggested for the treatment of the chronic diphtheria carrier state.

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THE EFFECTS OF BLOCKADE OF THE AUTONOMIC GANGLIA IN MAN WITH TETRAETHYLAMMONIUM

Preliminary Observations on Its Clinical Application*†

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The effects of tetraethylammonium, a quaternary ammonium ion, were essentially unnoticed until Acheson and Moe[1,2] recently demonstrated in animals that it blocks transmission of nerve impulses through autonomic ganglia. It is the purpose of this report to describe the effects of such an autonomic blockade in man and to indicate the preliminary observations of its usefulness as a diagnostic and therapeutic agent in various disease states.

Pharmacology. Little information has been recorded in the literature concerning the action of the tetraethylammonium ion. It was noted[5] that it was capable of preventing stimulation of ganglion cells by other quaternary ammonium compounds, and that it possesses a so-called "paralyzing nicotinic action."[6] Acheson and Moe have studied the effects of the drug on the isolated dog heart[1] and on ganglionic transmission in dogs and cats,[2] using as test responses the reactions of the blood pressure, heart rate and nictitating membrane.

Tetraethylammonium bromide injected intravenously in doses of 0.1 to 10.00 mgm./Kg. causes a prompt fall of arterial pressure in animals. The depressor response is not the result of a direct action of the drug on the arteriolar smooth muscle since while intravenous doses cause an increase in the volume of blood flow through the femoral artery, intra-arterial injections of comparable doses cause no change. The blood pressure response is not due to a central action, but does not occur in the absence of vasoconstrictor tone. The drug causes no further fall of pressure after destruction of the medulla or section of the cervical cord. However, if vascular tone and blood pressure are restored by stimulation of the cervical cord distal to the point of transection, tetraethylammonium again causes a depressor response. If blood pressure is maintained by continuous infusion of epinephrine or angiotonin, tetraethylammonium causes no fall of pressure. Thus the drug does not prevent the direct effect of epinephrine, and the site of action must therefore be assumed to be in the sympathetic ganglia.

To prove that this action is in the gan-

* Aided by Grants from the Life Insurance Medical Research Fund and from Parke Davis and Company.
† Presented Before the American Society for Clinical Investigation, Atlantic City, May 27, 1946.

glia, the effects of the drug on transmission in the stellate ganglia were studied. Heart rate responses to ganglionic block would be expected to depend upon the existing balance between vagal and sympathetic tone. The drug causes no change in the rate of the denervated heart. When vagal tone is relatively high, as in animals under morphine-chloralose anesthesia, an increase of heart rate is the usual response to tetraethylammonium. Animals under dial or barbital anesthesia, in which sympathetic tone is high, respond with a decrease of heart rate. Section of the preganglionic stellate connections in such animals with a high sympathetic tone causes a decrease of heart rate; tetraethylammonium will now fail to cause a further change. If the heart rate is maintained at a high level by repetitive stimulation of the *preganglionic* fibers, the drug again causes cardiac slowing. If, on the other hand, heart rate is maintained by electrical stimulation of the *postganglionic* connections of the stellates, no change in heart rate follows injection of the drug. The site of action is therefore localized in the ganglia.

Similar experiments have been performed with the vagus nerves, except that stimulation of the postganglionic fibers in the mammal is not feasible. That the vagal blockade produced by the drug is ganglionic rather than terminal is suggested by the failure of the drug to diminish or block the cardiodecelerator or depressor effects of injected acetylcholine.

The ganglionic site of action has also been demonstrated in the superior cervical ganglion. If a sustained contraction of the nictitating membrane of the cat is induced by preganglionic stimulation of the cervical sympathetic nerve, tetraethylammonium causes relaxation of the membrane. The contraction induced by postganglionic stimulation is not affected by the drug.

Large doses of tetraethylammonium cause death of experimental animals, apparently as a result of central respiratory paralysis. There is no curariform paralysis of muscles;[3] death is in fact preceded by generalized muscle tremors, resulting from the direct action of the drug in high concentration on peripheral nerve or striated muscle. Local tremors are always apparent around an intramuscular injection site. The LD_{50} of the bromide salt in mice is approximately 75 mg./Kg. intraperitoneally. Dogs have been killed by as little as 40 mg./Kg. intramuscularly.

Effects in Man. *Methods of Administration:* Tetraethylammonium has been administered as the bromide or the chloride salt.* These salts are soluble in water and withstand autoclaving. They have been most satisfactory when administered in a 10% solution. A transient, but apparently maximal effect may be produced by the intravenous injection of as little as 0.1 gm. Larger doses may cause no greater effects, but the duration is more prolonged and the effects of the autonomic blockade become more apparent. In general 0.2 gm. to 0.5 gm. have been injected intravenously. The intramuscular dose should not exceed 20 mgm./Kg. body weight.[9] Subcutaneous administration produces considerable discomfort at the site of the injection. This is also present to a minimal extent after the intramuscular injection, since some patients complain of a mild burning or tingling sensation followed by residual soreness at the site of injection. More discomfort is experienced with injections of higher concentration. Though the drug has been administered orally in doses of 4 to 6 gm., it produces very little physiological change even in patients who respond well to a parenteral injection. It is apparently poorly absorbed from the gastro-intestinal tract.

The Effects of Intravenous Injection: The intravenous injection produces a metallic taste in the mouth in 15 to 20 seconds. This is followed by a sensation of numbness and coldness of the hands and feet in about 25 to 35 seconds with

* Furnished by Parke Davis and Company, Detroit, Michigan, as Etamon, in 20 cc. sterile ampules through the courtesy of Dr. E. C. Vonder Heide.

subsequent paresthesia which quickly disappears. Shortly thereafter there is an incomplete dilatation of the pupil and a decrease in its reaction to light. There is some loss of accommodation. Ptosis of the upper eyelids occasionally develops. The patient feels "tired," "relaxed all over," "weak." Within 30 to 90 seconds there is a fall in both systolic and diastolic arterial pressures in the majority of patients with high arterial pressures and in some patients with normal blood pressure. (Fig. 1.) At the same time there is usually an elevation of the heart rate to between 90 and 120 beats per minute. Sweating, if present, stops. The mouth becomes dry. The temperature of the toes and fingers usually increases to that of the thigh or to about 33° C. The blood flow through the hands and feet as measured by the plethysmograph is increased. The systolic and diastolic pressures remain depressed for several minutes, then gradually increase to the initial level. Postural hypotension which develops immediately after the injection of the drug persists after the return of the blood pressure to its previous level and may last along with dilatation of the pupils and increased skin temperature for 15 to 60 minutes after a single injection. Vascular reflexes such as the effects of cold are abolished or greatly diminished at the height of the effects of the drug. At the same time there is cessation of propulsive gastro-intestinal motility so that barium in the gastro-intestinal tract may remain in the same position until the effects of the drug diminish. The bladder tone is diminished and the urge to void with bladder distention is lost. In spite of the fall in blood pressure there is a temporary increase in the cardiac output of about 20% as measured by the Starr type of ballistocardiograph in normal and in hypertensive subjects having essentially normal control ballistocardiographic waves. Normal subjects and patients with elevated venous pressures experience a significant decrease in venous pressure.

Effects of Intramuscular Administration: The intramuscular injection of 1–2 gm. will produce the same effects over a longer period of time. The arterial pressure may be depressed in hypertensive patients for 2 to 8 hours. (Fig. 2.) The skin temperature remains elevated and postural hypotension may persist over a longer period. The bladder atony becomes sufficiently pronounced so that the bladder may rise above the pubis, and the patient still has no desire to void. The gastro-intestinal tract remains quiet for several hours. During these effects, however, the patient is comfortable though there usually is weakness and faintness in the sitting position due to the postural hypotension.

Effect on Kidney Function: Though pronounced changes in the blood pressure may be experienced in patients with hypertension, there has been no evidence of impaired kidney function after the intramuscular injections. The urine volume is moderately reduced when there is a significant fall in arterial pressure. The renal blood flow has been measured in sixteen patients by the clearance of para-aminohippurate.[12] In normal subjects and in hypertensive subjects in whom moderate decreases in blood pressure were produced, clearance of para-aminohippurate* was not significantly changed. The glomerular filtration rate as measured by the clearance of sodium thiosulfate[11] was diminished in proportion to the fall in blood pressure.[7] In animals with neurogenic hypertension, induced by elimination of the buffer nerves, the decrease in blood pressure resulting from administration of the drug was not associated with any change in renal blood flow as measured by a flowmeter or by the clearance of para-aminohippurate. It would appear likely therefore that tetraethylammonium must induce in some cases a moderate renal vasodilatation since the renal blood flow is maintained as blood pressure falls. Vasodilatation is, however, apparently insufficient to maintain the renal circulation

* Sodium para-aminohippurate was generously supplied by Sharp and Dohme, Inc., Glenolden, Pa. through the courtesy of Dr. Karl Beyer.

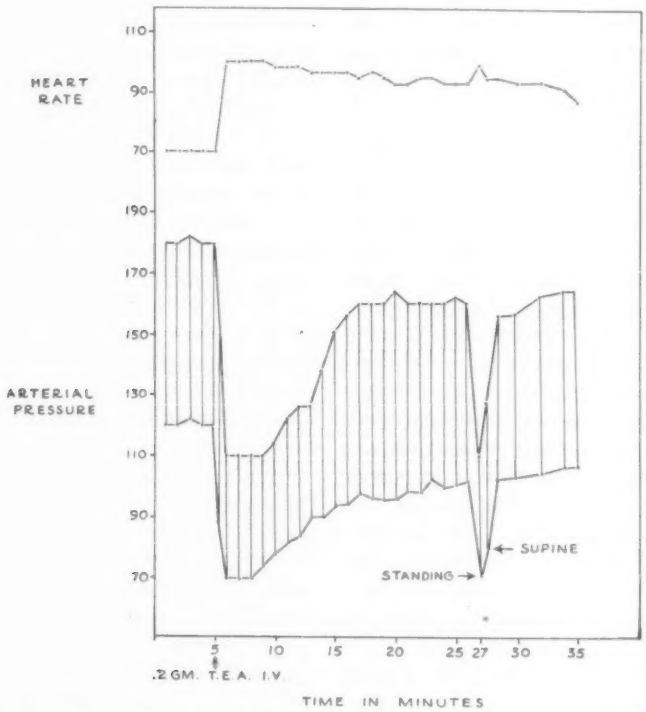

FIG. 1.—The intravenous administration of .2 gm. tetraethylammonium bromide produced a rise in heart rate from 70 to 95 beats per minute, with a fall in blood pressure from 175/116 to 110/70 mm. Hg. followed by a rapid return to the previous level with continued postural hypotension.

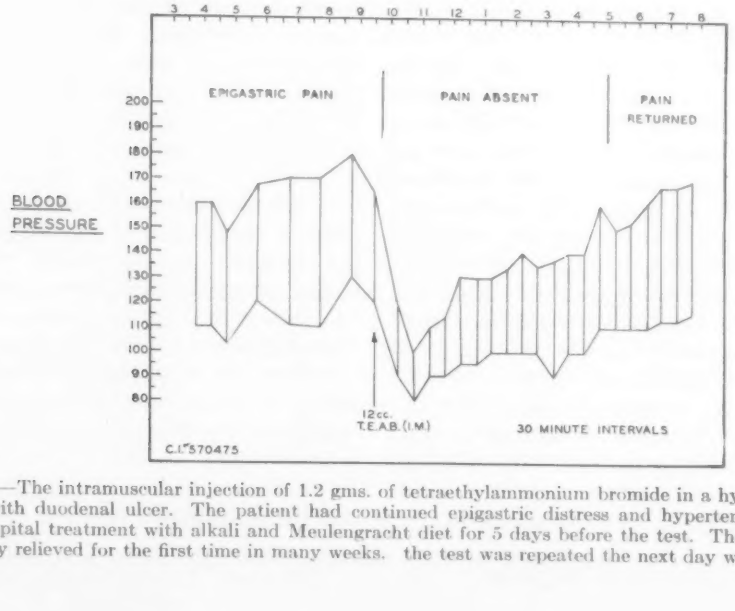

FIG. 2.—The intramuscular injection of 1.2 gms. of tetraethylammonium bromide in a hypertensive patient with duodenal ulcer. The patient had continued epigastric distress and hypertension while under hospital treatment with alkali and Meulengracht diet for 5 days before the test. The pain was completely relieved for the first time in many weeks. the test was repeated the next day with similar results.

during the sudden and profound reduction in blood pressure occasionally noticed after the intravenous administration of the drug in patients with very severe hypertension. Under these circumstances there has been a pronounced decrease in the renal blood flow and also a decrease in the formation of urine. This might be expected in patients with malignant hypertension where the organic renal arteriolar changes may be irreversible. It might also be explained as a result of peripheral circulatory failure which was suggested on some occasions.

Excretion of Tetraethylammonium: Tetraethylammonium appears to be almost quantitatively excreted in the urine. It can be recovered from urine by precipitation with Reinecke salt as in the determination of choline.[8] About 50% of the intravenous dose can be recovered in 30 minutes, while in 3 hours 50% of the intramuscular dose appears in the urine in the normal subject. Nearly all can be recovered in 24 hours. With oral administration only 6 to 15% can be found in the urine in 24 hours, suggesting that it is poorly absorbed from the gastro-intestinal tract.

Clinical Effects. It would seem from the above observations that the changes noted after the administration of tetraethylammonium are best explained by a blockade of both the parasympathetic and sympathetic nervous systems. The finding in animals of an increase in femoral arterial blood flow even in the presence of a fall in blood pressure, and the rise in peripheral skin temperature and blood flow in human subjects suggest obliteration of vasoconstrictor tone.

Peripheral Vascular Disease: The most striking clinical application has been in patients with arterial insufficiency of the extremities associated with vasospasm. The administration of tetraethylammonium has relieved this vasospasm so that even though there is a fall in blood pressure the skin temperature has increased to the same degree as that found after spinal anesthesia or after lumbar sympathectomy. (Fig. 3.) This has also been associated with dramatic relief of rest pain or intermittent claudication in a few cases. The vasoconstriction once relieved has, in some cases, failed to return. This has been especially striking in patients with Buerger's disease who have had continued relief of pain and a decrease in the inflammatory process following injections of the drug. In a few cases with obliterative vascular disease, pain has been relieved even though there was no change in skin temperature. The ability of tetraethylammonium to relieve vasospasm has made it a useful diagnostic tool in evaluating the role of neurogenic vasoconstriction in patients with arterial insufficiency who may be selected for lumbar sympathectomy. It has proven to be as reliable as paravertebral block or local nerve block.

Patients with thrombophlebitis and vasospasm have responded well with increase in skin temperature and, after repeated injections, a disappearance of the inflammatory process and edema. More details concerning its use in peripheral vascular disease has been presented.[4]

Causalgia: The drug has also been of value in relieving pain in many different types of causalgia and in post herpes zoster neuralgia. In a few instances the pain has been permanently abolished. In other cases pain has been relieved during the action of the drug and has been less severe as the effects of the drug disappeared. It has served as a useful diagnostic tool in the selection of cases of causalgia which might be relieved by sympathectomy.

Hypertension: The production of blockade of the autonomic ganglia is associated with a decrease in blood pressure, especially in hypertension. In normal subjects with initially low diastolic pressures there is little change in the blood pressure. In 143 hypertensive patients there was an average fall in diastolic pressure of 193. mm. and in systolic pressure of 23.5 mm. following injection of the drug. In spite of such a fall in blood pressure there has been relatively little change in the appearance of the retinal vessels.

It may be significant that 26 patients

with hypertension failed to have a fall in blood pressure with a test dose of the drug. In the majority of instances we have been unable to determine why these subjects failed to have the usual depressor response. A few of these subjects had uremia. Two had only one kidney, but most had the clinical diagnosis of essential hypertension. In some it is possible that epinephrine liberated as a result of apprehension over the injection and the frequent vomiting or temporary loss of consciousness and profuse perspiration even though the blood pressure may have fallen only to 150/90. Under these circumstances there is a drastic reduction in renal blood flow. Most of the patients recover spontaneously from this state within a few minutes. In some the subcutaneous administration of epinephrine has promptly restored the circulation.

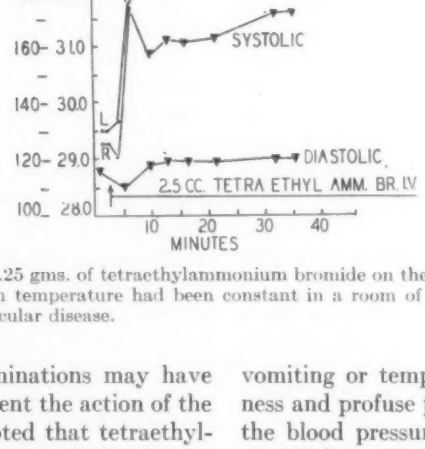

FIG. 3.—The effect of 0.25 gms. of tetraethylammonium bromide on the toe temperature of a hypertensive patient whose skin temperature had been constant in a room of 68° F. The patient had no evidence of peripheral vascular disease.

blood pressure determinations may have been sufficient to prevent the action of the drug. It has been noted that tetraethylammonium fails to overcome the pressor action of epinephrine. In a few cases repeated tests with an intramuscular injection were followed by a depressor effect when none had been noted with the initial intravenous administration of the drug.

In some patients with nephritis or in patients with essential hypertension and impaired kidney function the response to the drug was similar to that found in uncomplicated essential hypertension. A similar response has also been noted in toxemia of pregnancy. In one case of coarctation of the aorta there was not only a significant decrease in both systolic and diastolic pressure, but also a pronounced increase in skin temperature of the extremities. The older hypertensive patients seem to have a somewhat greater depressor response.

In some patients with malignant hypertension or with very severe essential hypertension there has been a profound fall in blood pressure followed by circulatory collapse. The collapse is accompanied by extreme weakness, drowsiness, yawning, and is associated with slowing of the heart, the development of nausea and, at times,

In a few hypertensive patients with severe nuchal headaches associated with an elevation of pressure above the usual level and with vertigo, nausea, vomiting, or recent impairment of vision, the administration of tetraethylammonium has been helpful in relieving these symptoms as well as in decreasing the blood pressure. In such cases and in some without symptoms the blood pressure failed to return to its

previous level after the administration of the drug. The decrease in blood pressure in these patients was of the same degree as that usually found after several days of hospital rest.

In a few patients with dyspnea and orthopnea associated with hypertensive heart disease and heart failure, the use of the drug was followed by a decrease in the severity of the symptoms. One patient with severe orthopnea, in spite of continued hospital treatment, was completely relieved for as long as twelve hours. Patients with nephritis and uremia as well as orthopnea were not relieved of their symptoms.

The decrease in blood pressure noted after such an autonomic blockade might suggest that it would be useful in the selection of hypertensive cases for sympathectomy. The blood pressure response to intravenous or intramuscular administration of tetraethylammonium has been recorded preoperatively in 51 patients subjected to supradiaphragmatic splanchnicectomy. At present an insufficient time has elapsed for the evaluation of the postoperative results. The blood pressure two weeks after the operation was somewhat similar to that found during the administration of the drug. In 13 cases the diastolic pressure failed to fall below 110 with the drug and in 11 of these cases it continued to be above 110 after the operation. In 38 cases the blood pressure fell to 110 or below with the drug and was found to be 110 or below in 28 cases two weeks after operation. In general there was a greater fall in blood pressure with the drug than that experienced two weeks after supradiaphragmatic splanchnicectomy. But a linear correlation of this relationship has been unsatisfactory up to the present time. This is to be expected, of course, since the sympathetic control of the extremities is not altered by this type of operation. The diastolic pressure two weeks after the operation represents, in general, the maximal effect of the procedure in lowering the blood pressure. An average increase in diastolic pressure in the next year of about 15 mm. of mercury can be expected.

Attempts have been made to maintain the blood pressure at a lower level by continuing the autonomic blockade with repeated intramuscular injections. This has caused moderate discomfort to the patient. When the drug was discontinued the blood pressure returned to its previous level.

Coronary Artery Disease: The possibility of the development of coronary ischemia and angina pectoris as a result of the sudden decrease in blood pressure in hypertensive patients was considered, but it has not been observed. In fact, the intravenous administration of the drug in 2 cases has dramatically relieved the pain of acute myocardial infarction in the presence of a significant fall in the blood pressure without the development of further changes in the electrocardiogram. Similar observations have been made in a few patients with angina pectoris at rest in whom no pain or change in the electrocardiogram developed with transient decreases in the blood pressure in one case from 170/110 to 60/40.

Though tetraethylammonium has relieved the pain of acute coronary thrombosis or angina pectoris, we do not have sufficient information at present to explain this action. It would not seem advisable to use it for this purpose until more details are available concerning its action on the coronary arteries in the presence of a fall in arterial pressure.

Gastro-Intestinal Tract: The cessation of gastro-intestinal motility observed fluoroscopically with the barium meal is also apparent clinically. In patients with pain resulting from a peptic ulcer the administration of the drug is followed by immediate relief of the pain and by a decrease in peristaltic sounds. (Fig. 2.) As the effects of the drug wear off pain returns and peristalsis may even be more rapid. In a similar manner abdominal cramps and diarrhea may be temporarily abolished by the administration of tetraethylammonium. It not only produces a cessation of gastro-

intestinal motility but also has significantly decreased the acidity and the volume of gastric juice in an unstimulated stomach. However, it does not alter the effect of histamine on gastric secretion.

Though it has favorably altered headaches in hypertensive patients, no effect has been noted in a few so-called migraine headaches. It has no analgesic effects on the usual types of somatic pain. A trial of the drug in eight patients with dysmenorrhea has not been successful in relieving the pain which suggests that the mechanism of pain is different from the muscle cramps of the gastro-intestinal tract.

Toxic Effects. Though the drug has been administered over 1000 times to more than 400 cases, very few serious effects have been noted. In a few hypertensive patients and those with generalized arteriosclerosis, there has been a severe fall in blood pressure associated with other evidence of peripheral circulatory collapse. The drug should be used cautiously in severe hypertension particularly when renal function is poor. In 4 subjects the extravascular injection of the drug in the antecubital fossa was associated with a flexor spasm which persisted for only a few hours and was apparently the result of local action of the drug on the nerve trunks. Four female subjects who received large doses of the drug developed a sudden onset of hyperventilation similar in many respects to hysterical hyperventilation with a further rise in pulse rate and blood pressure. They complained of difficulty with inspirations, possibly related to retention and drying of the bronchial secretion. This quickly subsided with no ill effects. In general, intravenous or intramuscular injections produce little change in respiratory excursions. Some have had an increase in respiratory rate for a few moments immediately after the intravenous injections. Respirations, of course, become very slow in those patients who developed peripheral circulatory collapse.

Some patients complained of dysphagia which was associated with profound dryness of the mouth, making it difficult to swallow.

In a few patients, the sensation of weakness and fatigue and light headedness was very pronounced; they appeared to experience difficulty with muscle movement though when tested there was no loss of strength or change in the muscle reflexes. The sensation is associated with dulling of the sensorium so that integration of movement is somewhat more difficult; speech is slowed but not impaired except by the very dry mouth. The patients have trouble explaining the sensation. This was experienced more often after repeated injections at short intervals or after large doses and occurred at times without a fall in blood pressure. The explanation of this apparent weakness is not clear, but it seems likely that it is of central origin. In animals depressor doses of the drug may increase the muscular response to electrical stimulation of the nerve; curariform action on muscles has been noted only after very large intra-arterial injections of the drug.[3] In some small patients who have received rapid intravenous injections of 0.5 gm. or more and in obese patients given large intramuscular injections, muscle tremors have been noted a few minutes after the injection. These are irregular in character, and usually quite transient. The patients describe it as a rigor similar to a chill though they are not cold.

Repeated intramuscular injections with resulting continued autonomic blockade produces a variety of complaints. The inability to void or to defecate at times alarms the patients. The loss of accommodation limits the patients' ability to read. The dry mouth is annoying. Many patients have a loss of appetite and in some a sensation of nausea. The postural hypotension is sufficiently severe so that the patient must remain supine. Some who have attempted to stand have, of course, felt very faint or have collapsed. In general continuation of the autonomic blockade longer than 36 hours has caused considerable distress to the patient.

Conclusions. 1. Tetraethylammonium administered to man in doses of 0.2 to 0.5 gm. intravenously or up to 20 mg./Kg. intramuscularly produces a series of changes which are best explained by blockade of the autonomic ganglia.

2. The effects on the cardiovascular system are primarily the result of the release of vasoconstrictor tone; there is an increase in skin temperature, a transient fall in both systolic and diastolic pressure, postural hypotension, a fall in peripheral venous pressure and an increase in heart rate and cardiac output. These effects have been applied clinically in peripheral vasoconstrictive states, in relief of pain due to ischemia, in the relief of vasospasm, and as a diagnostic procedure.

3. It produces a cessation of normal peristalsis in the gastro-intestinal tract and a diminution in gastric secretion. This has been applied clinically for the relief of pain and increased motility of the gastro-intestinal tract. There is also a decrease in salivary secretion, cessation of sweating, incomplete dilatation of the pupil with loss of accommodation. The tone of the urinary bladder decreases and the urge to void is abolished.

4. There has been significant relief of pain in causalgic states, which in a few instances failed to return after the immediate effects of the drug had disappeared.

5. Toxic effects have been chiefly due to the ganglionic blocking action of the drug.

6. Tetraethylammonium is a useful tool for the further study of disorders affecting the autonomic system.

7. It is helpful in the selection of patients in whom surgery on the autonomic nervous system is to be considered.

8. In selected cases the use of the drug may be of therapeutic as well as diagnostic value, especially in peripheral vascular and causalgic states.

9. Though it will produce a transient fall in arterial pressure and has relieved symptoms of the complications of hypertension in a few instances, treatment of hypertension by repeated use of the drug does not appear feasible.

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INSENSITIVITY TO EPINEPHRINE IN A PATIENT WITH A FUNCTIONING TUMOR OF THE ADRENAL MEDULLA

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The syndrome associated with tumors of the adult chromaffin cells of the adrenal medulla is well-known and excellent summaries[2,9,11] of the literature on this condition are available. However, the data pertaining to the important matter of loss of sensitivity to epinephrine in such cases are extremely meager. The effects of small doses (0.5–1.25 cc.) of 1:1000 epinephrine have been studied by other investigators.[4,7,10,11,12,13,14] No attacks followed, and few other data were reported. In none of these instances were the doses of epinephrine increased to the maximal level employed in the case we wish to report. We administered increasing doses of epinephrine both while the tumor was present and after its removal. Our results showed that the patient was definitely hyposensitive to epinephrine action while the tumor was present; this hyposensitivity disappeared after its extirpation. We also studied the patient's response to the administration of acetyl-β-methyl choline, and amyl nitrite, took electrocardiograms and ballistocardiograms before, during, and after attacks; determined changes in many of the chemical constituents of the blood; assayed the epinephrine content of the tumor; measured the urinary epinephrine; determined the amount of choline esterase in the blood, and measured muscle potassium content.

Case Report. J. G. was a 42-year-old white male who was well until 2½ years before admission to the Hospital, at which time he began to have attacks of palpitation (a slow, hard heart beat) headache, pain in the epigastrium, perspiration, lacrimation, and salivation. Each attack lasted from 30 minutes to 2 hours and while they occurred irregularly at first, about one year before admission the frequency increased until they were occurring from 1 to 16 times a day. In the more severe attacks, nausea and vomiting with back pain were present, and when the attacks were wearing off a feeling of swelling in the neck was frequently experienced with actual increase in neck size due to venous engorgement. These episodes were often brought on by physical exercise or changes in position such as lying down.

On physical examination there were no abnormalities save a few pigmented naevi from 2 to 5 mm. in diameter which were scattered over his trunk. His blood pressure on first examination was 130/80; blood pressure changes during a typical attack may be seen in Figure 1.

Numerous attacks were witnessed during his hospital stay. The initial phenomenon was a slow, forceful, and often irregular beat seen over all of the major superficial arteries. The extremities were then noted to be blanched and cold, and the patient began to perspire slightly. Distention of the small and deep veins of the neck became increasingly prominent as the attack progressed, while venipuncture of the forearm veins became difficult due to spasm. In the more severe attacks epigastric pain developed with nausea and vomiting. Salivation and lacrimation were seen early but soon disappeared. After the first phase of cardiac slowing to about 60 beats per minute the heart rate increased. No changes in the measurements of the pupils occurred. Swelling of the neck was obvious long after all other signs had disappeared.

Routine studies were as follows: a complete blood count, urinalysis, Kolmer and Kline reaction, and chest film, all with no abnormalities. The basal metabolic rate was +8 per cent. The values for the 100-gm

5-hour glucose tolerance test were: fasting 75, 1 hour 224, 2 hours 73, 3 hours 54, 4 hours 63, 5 hours 83 mgm/100 ml. Blood sugar values during an attack showed no striking rise (see Figure 1).

The intravenous urogram was reported as showing a slight lateral and downward displacement of the superior pole of the right kidney. In some of the films a vague, rounded mass could be seen medially and superior to the right kidney. Perirenal air insufflation was not attempted because of its potential dangers.

On September 13, 1945, the patient was operated upon by Dr. Jonathan Rhoads of the Surgical Service of the University Hospital through a right rectus incision under endotracheal cyclopropane anesthesia. The approach through the right side was chosen because of the suggestive findings in the urogram. A tumor of about the size of a tennis ball was found in the region of the right adrenal, while palpation of the left adrenal area revealed nothing abnormal. The tumor was quite adherent to adjacent structures and during the operation the capsule was torn, necessitating piecemeal removal. At one point during the operation the blood pressure rose to 320/160 and the pulse to 180, but on the whole the patient withstood the operation quite well. The blood pressure was well maintained after operation and, while no evidence of adrenal cortical failure developed, desoxycorticosterone was given prophylactically. Convalescence was uneventful. On examination five months later no complications or evidence of recurrence had developed.

Pathological report by Dr. R. C. Horn was as follows: "The tumor is highly cellular, having little stroma, composed almost entirely of delicate, but often large, capillaries. The tumor cells uniformly are large and more or less rectangular. The nuclei vary moderately in size but are usually ovoid and vesicular with a small nucleolus. The cells are arranged in clusters or in undulating cords with their long sides parallel. They show a striking tendency to be arranged perpendicularly, along or about blood vessels. The cytoplasm is usually stippled with fine granules which are blue in hematoxylin and eosin stains and brownish red in Trichrome preparations. There is considerable hemorrhage but in general the tumor is well preserved. The morphology is that of endocrine gland tumors in general and coincides with the usual pheochromocytoma or adrenal paraganglioma. Most of these tumors are benign and it is likely that this one is also. However, occasional bizarre, gigantic tumor cells and mitotic figures are present and tumor cells are seen in a few blood vessels. This latter finding may be without significance. Nevertheless, malignancy must be considered as a possibility, although unlikely. The skin lesion is a mole showing little pigmentation."

The total weight of the tumor was 42.8 gm. Except for the small samples taken for pathological studies, the pieces of tumor were immediately frozen in dry ice and sent to Dr. Carl Beyer of the Sharp and Dohme Laboratories and assayed for epinephrine content. The tumor contained 76.5 mg. of free epinephrine by the colorimetric method of Beyer and Shapiro.[1] No conjugated epinephrine was found.

At the time of operation a small piece of rectus muscle was removed and later analyzed for potassium content. This was found to be 172.0 m.Eq/Kgm. of wet muscle. According to Fenn's[6] review of the literature, the normal values for muscle potassium found in humans by Katz and others was 82 m.Eq/Kgm. of wet muscle.

Studies of the Attacks. As part of our study, an attempt was made to discover what stimuli were effective in producing an attack. The patient stated that emotion was not a factor. Injections of sterile water given before each testing were found to be ineffectual. Exercise or postural changes such as lying down usually produced attacks as described previously. Typical attacks were easily produced by having the patient bend and twist his waist or by pressing his knees into his abdomen. Manual massage of the adrenal area proved ineffectual.

The patient was given 10 mg. of acetyl-β-methyl choline subcutaneously to deter-

mine whether this drug would cause functional stimulation of the tumor. The effect of the administration of this drug was very dramatic, for, in addition to the usual acetyl-choline like effects, the patient had one of his most severe attacks. Atropine was not given to counteract the acetyl-choline effects, for it was feared that abolishing the depressant effects of the vagus on the heart might cause a disastrous increment of blood pressure. It was amount was increased to 1.0 cc. and 1.5 cc. with no detectable result except the usual pilomotor response at the site of injection. When 2.0 cc. were given, a slight rise in blood pressure occurred (to 162/98) but no symptoms were experienced. However, 2.5 cc. gave a blood pressure rise to 220/114 and the patient noted the symptoms that usually occurred with a mild attack.

The inhalation of a perle of amyl nitrite

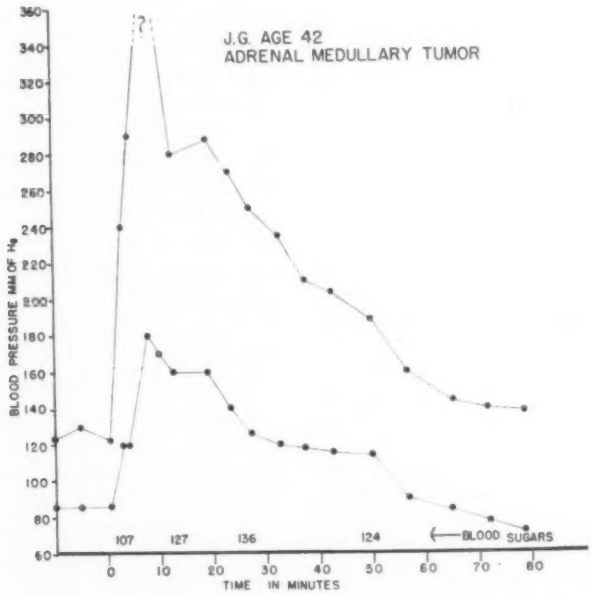

FIG. 1.—Variations in blood pressure and blood sugar concentration during an attack induced by exercise.

not deemed advisable to repeat the injection of acetyl-β-methyl choline because of the severity of the reaction.

The effects of epinephrine were next studied (Figure 2). The solution used was first compared with the U. S. P. standard epinephrine by Dr. H. D. Bruner of the Department of Pharmacology, and found to be of standard strength. The same solution was used throughout all tests.

When 0.5 cc. of 1:1000 epinephrine was given subcutaneously, no discernible effect on the patient or change in his blood pressure was noted even after vigorous massage of the site of injection. The was next tried in order to determine whether the resulting fall in blood pressure common to this compound and acetyl-β-methyl choline was a factor in producing an attack. Flushing, headache, and a fall in blood pressure of 40 mm. of mercury resulted, but no attack occurred.

Electrocardiograms were taken before, and 4, and 15 minutes after the onset of an attack. The standard limb leads were taken and in addition CR2, CR3, CR4, and CR5 leads. When no attack was present, the most striking changes were inversions of T-waves in I, II, and CR5, with low or flat T-waves in III, CR2 and

CR4. Four minutes after the onset of an attack, A-V nodal rhythm was present with a rate of 65 and the previously low or inverted T-waves were now elevated to normal or slightly above normal heights. Fifteen minutes after the onset of the attack the electrocardiograms had returned to the same form they showed before the attack.

Ballistocardiograms[16] were taken when no attack was present and at repeated intervals after an attack had been induced. The form of the records was normal when no attack was present, but the cardiac output was 52% above average normal. Four minutes after the onset of an attack, the form of the record was completely confused, and the amplitude relatively small. As recovery took place, the record gradually returned toward normal, but the form was now of the "late down-stroke type." This abnormality is characterized by a small I wave, often notched, and a prominent K-wave; these abnormal forms are frequently seen in patients with severe circulatory abnormalities. The results of additional studies are summarized in Table 1.

Postoperative Studies. Manipulation which had caused attacks before operation failed to do so after it. Ten mg. acetyl-β-methyl choline produced its usual response but no attack ensued. A most striking change was noted in the patient's reaction to epinephrine (Figure 2). After the injection of 0.25 cc. of 1:1000 epinephrine subcutaneously, a definite rise in blood pressure to 172/98 occurred with all of the previous symptoms of a typical attack. This time, however, he complained of nervousness which he had never experienced before even during his worst episodes. When the amount of epinephrine was increased to 0.5 cc. and 1.0 cc., a correspondingly greater rise of blood pressure and more severe symptoms occurred.

One month after operation the electrocardiograms were almost entirely normal, the only persisting deviation being a slight flattening of the T-waves in the limb leads. After the injection of 0.25 cc. of 1:1000 epinephrine subcutaneously, a tachycardia occurred with the development of flattening of the T-waves in all leads.

The ballistocardiogram one month after

Table 1.—Results of Various Analyses In and Out of Attacks

	Normal Range	No Attack Present	23 Minutes after Onset of Severe Attack
Serum Calcium mg./100 ml.	9–11	9.5	....
Serum Magnesium m.Eq/100 ml.	1.8–2.2	1.9	....
Serum Cholesterol mg./100 ml.	150–190	291	....
Serum CO_2 vol./100 ml.	50–71	61	50
Serum Chloride m.Eq/100 ml.	98.5–104.5	99.8	100
Serum Protein gm./100 ml.	5.9–7.0	5.6	5.9
Serum Total Base m.Eq/100 ml.	142–149	153.8	....
Serum Potassium m.Eq/100 ml.	3.8–4.3	5.0	2.9
Serum Urea Nitrogen mg./100 ml.	22–29	20	....
Serum Volume ml. (T 1824)	2000±	2400	....
Extracellular Fluid Per cent Body Weight (Thiocyanate)	20–28	27.3	....
Water Excretion Test, A Value (Robinson, Power, Kepler)	25+	4	....
Urinary 17 keto steroids mg./24 hour (Zimmerman)	12–19	6.1	....
Urinary Conjugated Epinephrine mg./100 cc.	0	0	0.45*
Plasma Choline Esterase† (micro mols of CO_2/30 min.)	10–18	13	....
Red Cell Choline Esterase† (micro mols of CO_2/30 min.)	9–13	10.2	....

* In 163 cc. urine collected during attack.
† Bodansky's modification of Ammon's method.

operation was normal in form, but the cardiac output had increased to +86%. Five months after operation, the cardiac output was still +43%. At this time the response of his circulation to 0.5 cc. of epinephrine given subcutaneously was the usual one seen, an increase in cardiac output of 40% above the base line value.

Comment. Although emotion did not produce attacks in our patient, other observers[18] have reported that emotion did serve as an inciting factor. Since a lack of physiological rapport with the rest of the body is one of the characteristics of all tumors, one wonders whether the attacks reported after emotional upset were due primarily to nervous stimulation of the tumor, or were instead secondary to pressure on the tumor. These tumors are usually directly under the diaphragm where they would tend to be compressed by the sudden deep inspirations of the changes in intra-abdominal tension consequent to excitement. Postural changes undoubtedly work through this same mechanism.

The reason for the effectiveness of the 10-mg. dose of acetyl-β-methyl choline in producing an attack is uncertain. The events may have been coincidental or they may have been secondary to massage of the gland by diaphragmatic action or changes in intra-abdominal tension. Kvale and Roth[5] found 2 mg. of acetyl-β-methyl choline ineffective in producing an attack in their patient, but did produce repeated attacks in 3 patients by the use of intravenous histamine.

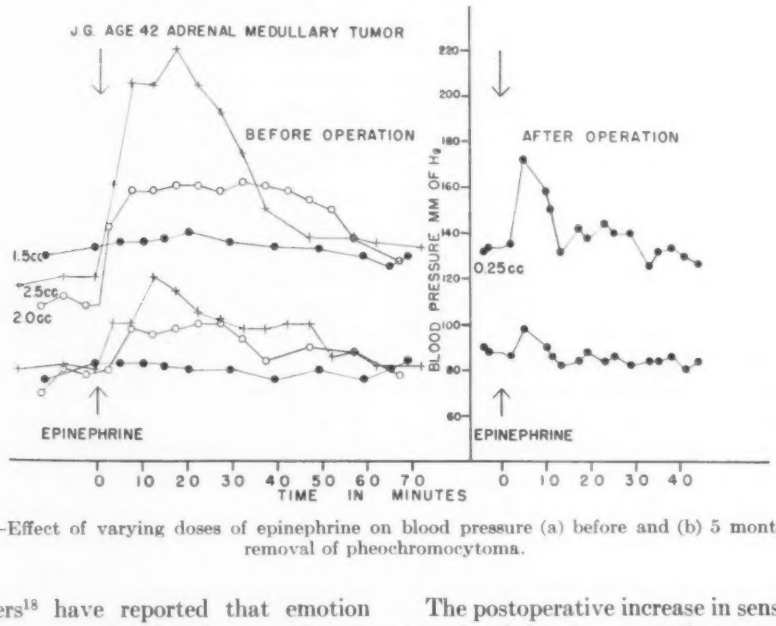

FIG. 2.—Effect of varying doses of epinephrine on blood pressure (a) before and (b) 5 months after removal of pheochromocytoma.

The postoperative increase in sensitivity to epinephrine in our patient was quite striking (Figure 2). As may be seen by the graph, 0.25 cc. of epinephrine given after operation produced a higher blood pressure rise than did 2.0 cc. before operation. It should be noted, however, that the rise in blood pressure was more sustained with the larger amount.

Although some pharmacologists[5, 15] do not believe that tolerance is developed to epinephrine, it is a well-known clinical fact that "fastness" to epinephrine occurs in asthmatics receiving large doses over a long period of time. The development of tolerance to epinephrine could perhaps be more reasonably anticipated in patients with functioning tumors of the adrenal medulla than in any other group, especially

if the tumor had been active for a long time. Strombeck and Hedberg,[17] using a a colorimetric method, reported that the blood epinephrine levels were 30 times normal in a patient with pheochromocytoma when no attack was present and the blood pressure was normal. Beer *et al.*,[19] using a rabbit ear perfusion, claimed evidence of increased vasoconstrictor action in blood drawn from his patient during an attack. These observations, together with the rapid fall in blood pressure which often occurs immediately after the removal of such tumors or even after interruption of their venous circulation, suggest that the normal pressor mechanism may undergo some type of compensatory adjustment to the constant or intermittent presence of large amounts of epinephrine in the blood stream.

The phenomenon of epinephrine resistance, if constant, should be of use clinically and might constitute a relatively harmless test for functioning adrenal medullary tumors. Since these tumors are so rare, it is impossible for any one group of investigators to collect more than a few cases, so experience must be built up slowly.

The electrocardiographic changes described by us have been reported by other observers[3, 8, 12] in cases of pheochromocytoma. The A-V nodal rhythm is best explained as a vagal phenomenon since other evidences of a parasympathetic discharge in the form of salivation, lacrimation, and perspiration were present. Elevation of the T-waves during the attack is, as far as we know, unexplained, and is the reverse of what might be expected to result from the fall in serum potassium concentration observed during an attack. The depression of the T-waves by epinephrine after operation in spite of a blood pressure rise suggests that the phenomenon is not due to the epinephrine alone, but some other factor must be present.

The ballistocardiographic abnormalities which developed during attacks were those which might have been expected with a heart working under heavy strain. After operation, the patient's temporary increase in cardiac output from +52% to +85% suggests an over-compensation of the heart after recovery from the strain of maintaining the repeated bouts of hypertension. Five months after operation, the cardiac output was once more near the preoperative level, +43%.

In our chemical analyses, we were able to confirm the findings of MacKeith,[11] that the serum potassium was elevated. This was only true when no attack was present, the value being significantly below normal during an attack. Another feature was the increase in muscle potassium to over twice the values given in the literature. These evidences of disturbances in potassium metabolism are quite striking and should be investigated in other cases. The serum changes may be of aid in recognizing the disease. The significance of these changes is still uncertain, but they suggest the possibility of intermittent variations in adrenal cortical function. This possibility is further supported by the decrease in urinary 17-keto-steroid excretion and the low A value in the water excretion test, although the patient did not present symptoms suggesting adrenal cortical failure.

Summary. 1. Insensitivity to epinephrine was demonstrated in a patient with a functioning tumor of the adrenal medulla.

2. A return of normal sensitivity to epinephrine followed surgical removal of the tumor.

3. The suggestion is made that the demonstration of such insensitivity may serve as a useful and harmless test for the diagnosis of such tumors.

We are indebted to Dr. Joseph Aspel for the opportunity of studying our patient. We wish to thank Dr. Carl Beyer, Dr. F. W. Sunderman, Dr. Julius Comroe, and Dr. H. D. Bruner for valuable contributions to our data. Dr. Isaac Starr contributed suggestions and reviewed the ballistocardiograms. Our electrocardiograms were reviewed by Dr. C. C. Wolferth.

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INCREASED REACTIVITY CAUSED BY ADRENALIN

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The action of prolonged administration of adrenalin in reducing the reactivity to the drug has already been reported (Cameron[2c]).

We have now observed instances in which the administration of adrenalin may have the reverse effect, namely, it may increase the reactivity of the individual to the drug. This communication consists in a report of such instances and an attempt to evaluate the light which they throw upon the development of the chronic tensional anxiety states. The phenomena observed fall into 3 groups: (*a*) Head and neck aches, (*b*) Increased cardiovascular activity, and (*c*) Venous phenomena.

Head and Neck Aches. Very severe headaches were noted in patients who were receiving intravenous and intramuscular adrenalin therapeutically. These patients were suffering from various degrees of tensional anxiety state and were being treated with injections of adrenalin which varied from .001 mg. to .09 mg. intravenously and from .4 mg. to 2.0 mg. intramuscularly (Cameron[2c]). Out of 42 patients receiving these injections over periods which ranged from 3 months to 2 years, 7 developed severe headaches: 3 patients had headaches on one occasion only, 2 patients experienced these headaches on 2 occasions, 1 on 6 occasions and 1 on numerous occasions over a period of 43 days.

Location. An outstanding feature of these headaches was their location. Without exception they involved the occiput and the back of the neck, extending, in several instances, in the form of an aching sensation as far down as the first dorsal vertebra. In 2 patients other areas were involved as well. One patient stated that the headache commenced in the frontal region, then was experienced primarily in the right side, but within one-half hour was complained of principally in the occiput and neck areas. One patient complained of aching in the left temporal region, as well as the occiput and neck.

Preliminary comment may be made of the occurrence of aching of the neck and occipital headaches in patients suffering from tensional anxiety states (Wolff,[8] Cameron[2b]).

Description. The headaches were invariably sudden in their onset, reaching full intensity within ½ to 1 minute after intravenous injection and within 4 to 5 minutes after intramuscular injection. In all cases the headache was primarily throbbing in nature; in 1 case it started as an ache but became throbbing within 20 minutes. The intensity was considerable, the patients looking alarmed and remaining motionless. In most instances there was an extension to the neck in the form of an aching stiffness and some pain on movement.

As to duration, apart from one mild headache which disappeared in 50 seconds, all the others lasted for periods ranging from 30 minutes to 8 days. The longer headaches persisted primarily in the form of an aching of the neck.

Relation to Cardiovascular Reactivity. The relation of these headaches to the reactivity of the cardiovascular system is important. The headaches most commonly appeared when the systolic pressure rose above 170 mg. Hg. and still more commonly when the difference between the pre-injection and post-injection pressures was more than 50 mg. Hg. (Table 1). The relative, rather than the absolute, rise seems to be the more important, since rises to 250 mg. Hg. have been elicited, without the production of headache, in hypertensive patients whose basic systolic blood pressures were over 200. It was noted, moreover, that the headaches were

more apt to appear when the blood pressure rise to a given dose had been greater than on previous occasions. Since, however, the blood pressure recording was not completed until the 90th second after injection and the headache had already set in by this time, it is not clear whether this greater response to the injection actually represented a greater reactivity or whether it was due to the anxiety produced by the headache. The reactivity of the pulse tends to be limited by the blood pressure rise and the most common immediate response was a slight brachycardia.

ance of the symptoms, but as the patient was not usually content simply to wait, more active measures were sought. It was found that a histamine hydrochloride solution, containing 0.1 mg. of the drug, given intravenously over a period of 6 minutes caused a disappearance of all complaints during the period when the patient was flushing in response to the histamine. These effects, however, were not permanent and after the histamine had been discontinued, the throbbing and aching tended to return in their former intensity. It was finally discovered that the most effective measures were deep massage of

TABLE 1.—APPEARANCE OF HEADACHE IN REPSONSE TO INTRAVENOUS INJECTION OF ADRENALIN

Miss N. S. March 25, 1945

	Time	B. P.	Pulse	Remarks
Initial Recording . . .	2 P. M.	116/76	72	Feels well save for a cold. Has had no anxiety attacks even though she missed a treatment during the week.
1st injection				
1 min.	2-15	140/72	72	
10 min.	....	114/74	63	
Amount 0.04 mg.				
2nd injection				HEADACHE—in back of neck. Began in
1 min.	2:25	196/106	72	less than 2 mins. after injection. Not a
10 min.		128/80	64	throbbing headache—located posterior to
Amount 0.07 mg.				left sternocleidomastoid. Seems to disappear with massage of area.
3rd injection				Throbbing in same area after third in-
1 min.	2:40	160/96	63	jection. Aching. 25 mg. papaverine
10 min.	2:43	130/90	78	hydrochloride intravenously.
Amount 0.04 mg.				
4th injection				
Not given	3:12	114/88	69	Neck not aching—but sore. Otherwise feels fine.

Note:—(i) Large rise in B. P., with headache, in response to second injection.
(ii) After headache appears, response to 0.04 mg. adrenalin hydrochloride is substantially greater than before headache. (Compare 1st and 3rd injections).

Alleviation. A number of agents were employed in an attempt to alleviate the head and neck aching, and in the anticipation that they might throw further light upon the mechanism involved. Sodium nitrite (gr. 1 to 3) by mouth and papaverine hydrochloride (mg. 16 to 64) intravenously were found to be of little value. Aspirin, and intravenous sodium amytal, gr. 7½, were found to reduce the patient's complaints, but there was no indication that this was due to control of the factors directly producing the aching.

As implied earlier, rest, for several days if necessary, resulted in a gradual disappear-

the muscles in the occipital area and along the back of the neck, together with the application of radiant heat. Under these circumstances, relief of the head and neck aches appeared rapidly and was considerably more lasting than that following the use of the other agents.

Increased Cardiovascular Activity. Of special significance is the subsequent reactivity of the cardiovascular system. In all instances it was found that the reactivity of the blood pressure and the pulse to adrenalin was considerably increased and often increased over a period of several days. This is in marked contrast to the

fact that repeated administration of adrenalin over extended periods tends to reduce the reactivity of the pulse and blood pressure to adrenalin (Cameron[2c]).

It was found in addition, that once headache had been produced it was almost impossible to give the same dose of adrenalin on a subsequent occasion during that day without eliciting another attack of headache. Indeed, in most patients, as long as 3 days after the headache had first appeared it was necessary to use a dose of adrenalin reduced by 50%. Before this had been recognized, our attempts to continue treatment at the same dose level perpetuated attacks of headache in one patient over a period of 43 days. Ultimately, in this case, it was necessary to reduce the dose to one-fifth of the original.

The observation was also made that, in almost every instance, for several days after the headache had been elicited the reduced dose of adrenalin would produce a considerably greater blood pressure rise than it had on earlier occasions. It was also observed that, in the majority of the patients, for several days after a headache had been elicited the basal pulse and blood pressure levels were greater than they had been (Table 2).

Venous Phenomena. Concurrently, with the investigation of these headaches, observations were made upon venous reactions which appeared in some patients, regardless of whether or not headaches were present. It was found that where it was necessary to use small and superficial vessels, particularly those on the front of the wrist, to inject the adrenalin, transitory changes appeared in these veins. The changes took the form of the appearance, within about 10 minutes after injection, of white streaks which followed the course of the vein and often extended from four to five inches up the arm, with occasional branching out for shorter distances. In some instances the streak extended back from the point of injection for about ½ inch, and in a few instances spread out from the sides of the streak in pool-like form, starting about 1 to 2 inches above the point of injection. In almost one-third of these cases, goose pimples appeared along the course of the white streaks. The goose pimples usually disappeared fairly soon after the injection, but the white streaks would persist as long as 5 hours. With subsequent injections of adrenalin at 10-minute intervals in the same vein, the streaks tended to

TABLE 2.—CONTINUANCE OF INCREASED REACTIVITY OF PULSE AND BLOOD PRESSURE ON FIFTH DAY AFTER APPEARANCE OF HEADACHE—SEE TABLE 1.

Miss N. S. March 30, 1945.

	Time	B. P.	Pulse	Remarks
Initial recording . . .	2:10	138/90	88	No panic attacks in past week.
1st injection				
1 min.	2:20	148/88	78	No headache.
10 min.	....	144/90	84	
Amount 0.02 mg.				
2nd injection				
1 min.	2:32	156/84	75	
10 min.	....	136/80	84	
Amount 0.03 mg.				
3rd injection				
1 min.	2:45	152/84	84	
10 min.	....	140/70	80	
Amount 0.04 mg.				
4th injection				
1 min.	2:59	154/84	81	
10 min.	....	130/80	76	
Amount 0.04 mg.				

Note:—(i) Initial blood pressure and pulse substantially higher than before the headache on March 25, 1945. (Compare initial readings in Tables 1 and 2).

(ii) Blood pressure and pulse rise is now slightly greater in response to 0.02 mg. adrenalin hydrochloride than it was to 0.04 mg. (Contrast first injection on Table 1 with first injection on Table 2).

become more pronounced and to extend further.

It was found that the streaks could not be eliminated by producing passive venous congestion of the arm, save that their color became temporarily lost during the period that the arm was cyanosed, reappearing again as soon as the congestion had disappeared. They could, however, be eliminated entirely by injecting a solution of histamine hydrochloride, containing 0.1 mg. of the drug, for a few minutes into the vein which had been used for the adrenalin administration. There seemed to be no reason to doubt that the white streaks represented changes in the vein itself and in some of its branches. The pooling effect was less clear. It did not appear to be due to the leakage of adrenalin from the point of injection, since it usually occurred 1 to 2 inches above this. The appearance of goose pimples in the skin along the course of the vein suggested, however, that either a transudation of the solution from the vein might occur, or that there might be a radiation of its constrictor effect from the walls of the vein to those muscular structures lying outside it which control the appearance of goose pimples.

Discussion. Our attempts to assess the significance of these observations upon head and neck aches, upon cardiovascular reactivity and upon the venous phenomena consequent to the injection of amounts of adrenalin apparently excessive can only be tentative, since there are still many gaps in our information.

The issue of primary importance which emerges from these observations is that the effects of excessive adrenalin administration may persist long after its general pressor action has disappeared. The significance is derived from the possibility that it may advance our knowledge of the development of the chronic tensional anxiety states.

How far are the mechanisms involved in the 3 groups of observations related? The effects, as far as the veins are concerned, appear to consist in a spasm of the muscle elements in their walls which may persist for several hours and, on occasion, may extend to the muscle structures of the overlying skin responsible for the production of goose pimples. This explanation is rendered the more probable by the fact that the goose pimples and the blanching can be completely abolished by the injection of histamine, which acts to relax muscular contraction in considerable areas of the cardiovascular system (Goodman and Gillman[3]).

The mechanisms involved in the head and neck aches appear to be more complex. It is necessary to consider not only the cause of these symptoms but also the explanation of their location. The fact that the headaches are at first primarily throbbing in character, that they appear coincidentally with excessive blood pressure rises and that they tend to disappear, though only transitorily, during the administration of histamine, suggests that they are vascular in origin and may be related to spasm of the arterial musculature. On the other hand, the fact that they tend to merge ultimately into an aching of the neck, and that they can be most readily overcome by heat and massage suggests that they may, at least in part, be due to spasm of skeletal muscle in those areas.

The question as to why these effects of activity should appear primarily in the occipital and neck regions is difficult. It may be said, however, that many tensional anxiety patients who have not received adrenalin complain in lesser degree of just such symptoms. It would appear that the scalp and the neck musculature are areas in which increased tension readily occurs. To this must be added the fact that they are areas subjected to frequent stimulation, the first through the participation of the scalp musculature in changes in emotional expression of the face, and the neck musculature through turning movements of the head.

Of still more importance is the fact that, in states of increased tension, the flexor musculature of the body tends to exert a

greater pull than the extensor. This produces the well known bowing of the back, bending at the knees and elbows and the bending forward of the neck. Hence the support of the head is thrown primarily upon the extensor musculature of the neck. Thus it is clear that, in the tensional anxiety cases, the musculature of the scalp and that of the back of the neck (which runs up for its attachment into the occipital area) are under special stress and for that reason may be presumed to be particularly likely to go into spasm when subjected to further sudden increase in tension, as during adrenalin administration.

The observation that, immediately following upon the administration of an excessive dose of adrenalin and in some instances for several days thereafter, the cardiovascular system reacts by the development of increased pressor response to further adrenalin administration and by increased basal blood pressure and pulse levels suggests that the reactivity of the muscle elements of the cardiovascular system has been increased.

Hence, it will be seen that the mechanism involved in all 3 groups of phenomena appears to be an increase in the reactivity of those muscle structures which ordinarily react to adrenalin. We have no evidence as to whether or not there is an increased reactivity of the other structures which react to adrenalin: of the secretory tissues and perhaps the central nervous system.

Here we wish to emphasize a point of fundamental importance, which, because our medical thinking is still dominated by the determinism of physics, we find it hard to keep steadily before us. Adrenalin, like any other agent, produces in the living organism an immediate reaction and may, as here, produce a change in the reactivity of the structures upon which it acts.

It is this increased reactivity which is of prime significance, in that it may afford us insight into the development of the chronic tensional anxiety reactions and the ultimate establishment of the autonomous anxiety state (Cameron[2a]) which has analogies with the concept of "structuralization" of the repetitive neurotic mechanism (Kubie[4]).

We are already aware that patients suffering from these states are more reactive to the injection of adrenalin (Maranon,[5] Backova,[1] Richter,[6] Thorley[7]) and that such injections cause a transitory reactivation of many of their complaints, and by no means only those related to increased muscular tension, so that the patient will often comment anxiously that we have brought back all his symptoms (Cameron[2c]).

Here, in these 7 patients, one sees that an excessive stimulation of the muscle structures which ordinarily react to adrenalin causes an increase in their reactivity which may persist over several days, and which, in one case in which the excessive stimulation was frequently repeated, persisted over a period of 43 days.

It seems reasonable to compare these findings with the situation which exists where the individual is exposed to repeated psychic traumata with repeated participation of the adreno-sympathetic system, such as occurs in combat experience or in prolonged involvement in a guilt or other conflict situation. In these situations, as in that presented in this report, there frequently results an increased reactivity of those structures which react to the adreno-sympathetic system. But these two situations differ in that the psychic traumata are repeated over long periods and lead, in a proportion of cases, to such a degree of increased reactivity of those structures which react to the adreno-sympathetic system that they eventually respond excessively to ordinary everyday stresses, thus resulting in the establishment of a self-perpetuating autonomous anxiety state (Cameron[2a]).

In the cases presented in this report, stimulation was limited to a few occasions and no lasting increased reactivity resulted, though there is evidence in at least one case that repeated stimulation would result in more lasting increased reactivity.

Summary. Administration of excessive amounts of adrenalin may result in severe head and neck aches, in transitory blanching of the injected vein together with the appearance of goose pimples, and in the persistence for several days of an increased pressor response to adrenalin. The mechanism of these symptoms is discussed and their relationship to the production of the chronic tensional anxiety state is considered.

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THIAMINE CIRCULATION TIME

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The use of thiamine hydrochloride as a new method for the determination of the circulation time was the subject of a preliminary report.[5] It was shown that the nut-like taste and smell of the drug gave arm-to-tongue or arm-to-nose circulation times in normal adults of 5 to 12 seconds. Since these values were much below others recorded in the literature,[4] by the use of other subjective and objective methods (Table 1), the effects of dosage and volume upon the circulation time were also studied.[7] The conclusions were that increasing doses speed the response until the "true" circulation time is reached (Fig. 1), and that thiamine gives shorter values, with optimal dosage of 100 to 300 mg. or more, than the maximum safe doses of magnesium sulphate, aminophylline, or decholin. Furthermore, volumes of solution 5 cc. or greater, which are often used clinically, as in the decholin method, have the mechanical effect of shortening the circulation time by 1 or more seconds.[7] The purpose of this paper is to report the determinations of thiamine circulation time in 295 cases of various conditions and to discuss certain factors which affect the measurement of circulation time in general.

To eliminate the volume and dosage factors,[7] all measurements were made with 1 cc., containing 300 mg. of thiamine hydrochloride,* injected rapidly intravenously, and timed from the beginning of the injection to the moment the subject first signified the taste or smell of the drug. Most patients tasted and smelled the drug simultaneously, but others noted taste or smell alone or one soon after the other. On rare occasions the taste or smell recurred faintly, as from recirculation, or, on the other hand, as if the first quick faint end-point indicated arrival at the lungs with perception of the drug in the expired breath. Complete failure to taste or smell the drug occurred in 13 of 295 cases, and obviously false high readings, up to 120 seconds, occurred in 9 others, particularly in cases of congestive heart failure. Some of this group responded, with reasonably low readings, when the dosage was increased above 300 mg. up to 600 or 900 mg. (2 or 3 cc.), but they are not included in our data. Check determinations with magnesium sulphate or decholin were obtained in most cases and gave, on the average, readings 4 to 20 seconds longer, expecially in heart failure, and about the same percentage of total failures.

Ninety-two normal adults tested by this method showed circulation times of 5 to 13 seconds, most of them 7 to 10 seconds (Fig. 2). Repeated determinations a few hours apart checked usually within 1 or 2 seconds. Post-prandial readings were little or no lower than fasting, but circulation times in the vertical position were usually 1 to 3 seconds shorter than in the horizontal.[6] Complete failures in this group of normals occurred in 4 additional cases, and false high readings of 25 and 120 seconds in 2 others. Four of these 6 individuals were over 60 years of age. Seventeen normal children, aged 5 to 12, responded in 4 to 8 seconds.

Patients with heart disease were subdivided into 4 functional classes, according

* Specially prepared in 10-cc. vials by E. R. Squibb and Sons.

to the Criteria of the New York Heart Association, in tabulating the results (Fig. 2). Five children with rheumatic heart disease, but without congestive heart failure, had circulation times within normal limits, 4 to 8 seconds. In 1 child with severe congestive heart failure (Class IV), the circulation time was 15 seconds. Sixty-five adults with organic heart disease but without congestive heart failure (Class I) had circulation times of 5 to 20 seconds, but only 4 of the 65 showed values beyond the normal limit of 13 seconds. It is quite possible, that these 4 patients were wrongly judged clinically to be in Class I instead of Class II. There was no apparent corre-

TABLE 1.—NORMAL CIRCULATION TIMES BY VARIOUS METHODS

Substance	Effect at	Circ. time (secs.)	Authors
Diodrast	Left ventricle	6–9	Robb and Steinberg, 1938
Thiamine	Tongue and nose	5–13	Ruskin and Decherd, 1945
Lobeline	Carotid sinus	6–13*	Piccione and Boyd, 1941
Radioactive sodium	Other arm (children)	5–17	Hubbard et al, 1942
Fluorescein (ultraviolet)	Conjunctiva	7–15.6	Fishback, 1941
Calcium chloride	Tongue	9–15	Kahler, 1929
Magnesium sulphate	Tongue	7–17.8	Bernstein and Simkins, 1939
Saccharin	Tongue	9–16	Fishberg et al, 1935
Decholin	Tongue	10–16	Tarr et al, 1933
Calcium gluconate	Tongue	10–16	Goldberg, 1936
Aminophylline	Medulla	7.1–20.4	Koster and Sarnoff, 1943
Methylene blue (photoelect.)	Skin	7–21.6	Jablons et al, 1944
Phenoltetraiodophthalein	Femoral artery	10–18	Hamilton et al, 1932
Magnesium sulphate comp. (Macasol)	Tongue	5–24	Kvale and Allen, 1939
Sodium cyanide	Carotid sinus	9–21	Robb and Weiss, 1933
Thorium-X	Other arm	10–20	Gerlach et al, 1943
Radium-C	Other arm	12–23	Blumgart and Weiss, 1927
Fluorescein (ultraviolet)	Lip	15–20	Lange and Boyd, 1942
Papaverine	Medulla	15.4–27	Elek and Solarz, 1942
Histamine	Skin	13–30	Weiss et al, 1929

* Add a minimum of 1 second for injection time.

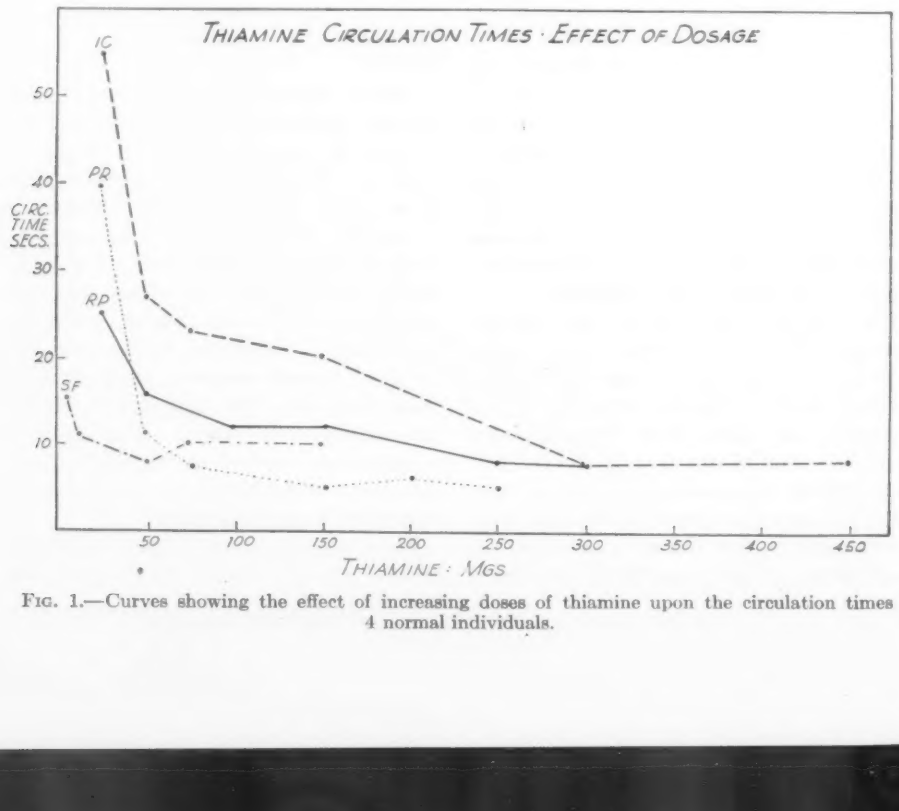

FIG. 1.—Curves showing the effect of increasing doses of thiamine upon the circulation times of 4 normal individuals.

lation between circulation time and roentgenographic evidence of enlargement of the heart in this group, contrary to Nylin.[3] Thirty-one patients in mild (Class II) failure had circulation times of 8 to 25 seconds; 23 in moderate (Class III) failure, 10 to 50 seconds; 17 in severe (Class IV) failure, 13 to 55 seconds. There were 2 other words, some cases of predominant left heart failure may be expected to show circulation time values considerably longer than those of right heart failure alone.

Five cases in moderate or severe congestive failure given 1.2 mg. of digitoxin by mouth, were tested every 2 to 3 hours and showed the first definite lowering of

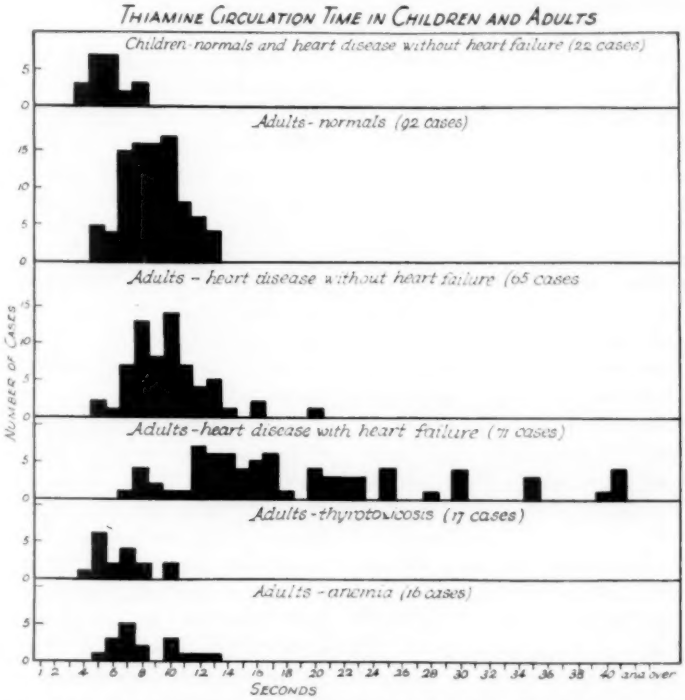
THIAMINE CIRCULATION TIME IN CHILDREN AND ADULTS
Children - normals and heart disease without heart failure (22 cases)
Adults - normals (92 cases)
Adults - heart disease without heart failure (65 cases
Adults - heart disease with heart failure (71 cases)
Adults - thyrotoxicosis (17 cases)
Adults - anemia (16 cases)
NUMBER OF CASES
SECONDS

FIG. 2.—The circulation times in various patients, with and without heart disease, obtained by the injection of 300 mg. of thiamine hydrochloride.

outstanding exceptions; one case of marked emphysema and another of old hypertensive heart disease, both in severe right heart failure without any pulmonary congestion. Each had a circulation time of 7 seconds. Other cases of cor pulmonale, including those in whom systemic venous congestion had superseded pulmonary congestion, account for many of the lower values in the entire congestive failure group. Considering that the pathway of any drug employed to measure the "total" circulation time involves the small vessel circuit in the lungs and not in the periphery, these results are not surprising. In the circulation time (by 3 or more seconds) in 4, 7, 9, 10 and 12 hours, respectively. This increased rapidity of blood flow is presumably to be correlated with the expected increase in cardiac output and in the first signs of improvement in the patient's functional status.

The effect of exercise up to the point of dyspnea, using the Master two-step equipment, tended to reduce the circulation time 1 to 3 seconds both in normal individuals and those presenting various degrees of congestive heart failure. There were no instances of significant prolongation after exercise in either group. The

attempt to distinguish early congestive failure from other conditions producing subjective dyspnea by means of the effect of exercise upon the circulation time would thus appear to be doomed to failure.

Nine cases of anasarca due to cirrhosis of the liver or nephrosis had normal circulation times of 7 to 13 seconds. Sixteen cases of moderate to severe anemia of various origins had circulation times of 5 to 13 seconds, the majority being 6 to 8 seconds. One case of sickle cell anemia with moderate congestive heart failure responded in 7 seconds, as did another, who in a previous crisis without heart failure had a circulation time of 5 seconds. There was no apparent correlation between the degree of anemia and rapidity of blood flow. Seventeen cases of thyrotoxicosis presented the expected accelerated circulation times of 4 to 10 seconds, 12 of them being 5 to 7 seconds. Again there was no correlation between the basal metabolic rate and circulation rate. Two cases of moderate (treated) myxedema had circulation times of 12 seconds. Two cases of high fever responded in 6 and 7 seconds respectively.

Comment. For more complete discussion, the reader is referred to one of our previous papers on the subject.[7] In view of the widespread measurement of the circulation time, especially as a method of diagnosing and following-up cases of congestive heart failure, certain points require particular emphasis. First, the usual doses of magnesium sulphate, calcium gluconate, and decholin used in clinical practice, may, and frequently do, give false high readings of the circulation time. That may be true even of 1-gram doses of magnesium or calcium salts. It has been common experience to get faint pharyngeal burning following the injection of one of these drugs in as long as 60 to 150 seconds, values that are obviously too high even for severe congestive heart failure. When large volumes of solution are used, the error may be the other way, that is, toward a quicker response.

Second, the so-called objective methods, involving the detection of dyes, radioactive substances and deepening of respiration, also give "normal" readings that are much too high (Table 1) and need restudy from the standpoint of the influence of dosage, volume and, perhaps, other unknown factors, before valid acceptance clinically. Furthermore, when these methods are applied to the study of peripheral arterial or venous obstruction, or congestive heart failure, that is, where either slowed blood flow or long circuitous pathways are involved, false high readings are again to be guarded against. Our own experiences[6] with the objective methods involving the production of the inspiratory gasp have been disappointing in the high incidence of total failures and indefinite and false high readings. That has been particularly true of the aminophylline method, the papaverine method,[1] and the use of nikethamide.

Nikethamide, one of the better known respiratory stimulants, can be used in a dose of 3 cc. of the 25% solution* intravenously as a measure of the circulation time, particularly in children.[7] The inspiratory gasp and, at times, a subjective burning of the face, occur in 6 to 9 seconds in children and in 7 to 12 seconds in most adults. However, in a total of 69 cases, 10 failures to obtain a clear end-point and 5 false high readings were encountered. The failures occurred particularly in cases of congestive heart failure, in which the drug would have been most useful, so that the method was abandoned.

The ideal method for the measurement of the speed of blood flow should be simple, objective, safe, and exact; this is yet to be found. The thiamine method has the disadvantage of requiring the cooperation of the subject and the injection of rather large doses of the drug. It has the advantages of simplicity, safety, and exactness. In case of failure to respond to the 300-mg. dose, 600, 900 mg. and even larger doses may be safely injected. To prevent another failure or delay in

* Generously supplied to us by Lakeside Labs., Milwaukee, Wisc.

response, an interval of at least 2 hours between injections has been found satisfactory.[7] Oral medication of thiamine or brewer's yeast and the fetor of suppurative bronchopulmonary disease have not affected the taste and smell of the injected thiamine in our subjects.[6] No serious allergic or anaphylactic reactions to the drug have been encountered by us in more than a thousand injections, except one case of mild urticaria in a person who had received therapeutic injections of "Betalin" a few months previously. A few serious reactions have, however, been recorded in the literature, including 2 deaths ascribed to repeated intravenous use of the drug.[2] Some reports of toxic reactions have emphasized the importance of a preliminary skin test as well as the avoidance of an interval of 1 or 2 weeks between injections as prophylactic measures.

Summary and Conclusions. 1. Thiamine hydrochloride, in a standard supra-optimal dose of 300 mg., is a safe and more exact subjective method for determining the speed of blood flow from arm to tongue.

2. The normal circulation time by this method is 4 to 8 seconds in children and 5 to 13 seconds in adults. Studies have been made in 295 different cases, and values recorded for various grades of congestive heart failure and other disorders.

3. Circulation time by any clinically used method varies inversely with the dosage of the drug until a point is reached which may be called the true or shortest circulation time.

4. This point is usually reached at a dose level of 200 to 300 mg. of thiamine, and may not be reached at the maximum safe dosage of 1 gram of magnesium sulphate, 0.48 gm. of aminophylline, or 5 cc. of 20% decholin.

5. Another source of error in doing circulation times with volumes of solution 5 cc. or greater is the shortening apparently resulting from the rapid injection of these amounts under pressure.

6. The ideal method for determination of circulation time should be simple, objective, safe, reproducible, and one employing constant dosage, which would be supra-optimal for all individuals. Such a method is yet to be found.

ADDENDUM: Since the submission of this paper an unknown component of vitamin B complex (Swenson, R. E.: Am. Heart J., **32**, 612, 1946) has been proposed as resulting in a characteristic taste which makes it useful as a method of arm-to-tongue circulation time. This substance, as indicated in this and our previous paper, is probably thiamine.

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THE ELECTROCARDIOGRAPHIC CHANGES CAUSED BY HYPERVENTILATION

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Since the observations by Yandell Henderson that hyperventilation induces circulatory and neurologic disturbances due to the hypocapnia and gaseous alkalosis, numerous reports on the effect of hyperventilation on the electrocardiogram have appeared.[4,7,8,9,10,16] These electrocardiographic alterations were usually attributed to the chemical changes provoked by overventilation.

However, it has been observed that alkalosis may be present without the appearance of alteration of the waves in the electrocardiogram and conversely that significant electrocardiographic changes may be present without alkalosis;[16] moreover, no parallelism need exist between the degree of the electrocardiographic changes and the extent of the alkalosis.[4]

In view of these discrepancies, we decided to re-investigate the influence of hyperventilation on the electrocardiogram. This seems to have practical importance since hyperventilation is not an uncommon event in patients whose electrocardiogram is taken, especially when pain and anxiety connected with cardiac disease are present. The fear of electricity is widespread and frightened patients may hyperventilate during the application of the electrodes. Furthermore, alkalosis does occur in manifold conditions; an example is the alkalosis following the ingestion of large doses of alkali. The changes in the electrocardiogram attributed to alkalosis were in some reports rather striking and an awareness of these changes is necessary if confusion with the abnormalities due to intrinsic cardiac disorders is to be avoided.

Method of Study. All subjects were hospitalized medical patients who showed neither clinical nor electrocardiographic evidence of cardiac disease. All lay quietly and flat in bed during the examination in order to eliminate positional effects on the electrocardiogram. Four types of experiments were performed: 1. Hyperventilation was done by means of slow and deep respiratory excursions which did not produce tetany or alkalosis. The respiratory rate averaged 10 per minute and this type of breathing was continued for 3 minutes. The carbon dioxide combining power was obtained before and after hyperventilation on most of these patients. This was done on venous oxalated blood by the Van Slyke gas analysis method.

2. Hyperventilation was performed by means of rapid and deep respirations until tetany and alkalosis were produced. The respiratory rate averaged 30 per minute and was kept up at this rate for 5 to 15 minutes until symptoms of tetany appeared.

Determinations of the pH of the blood were made on 10 successive patients. This was done on venous blood serum, collected under oil and centrifuged at a high speed for 5 minutes. Calculations were done by means of a Cambridge cathode electron ray pH meter with a McGuiness electrode.

3. The patient was ordered to perform very shallow and very rapid respirations, averaging 100 per minute, for 2 to 3 minutes. The breathing was of the costal type, predominantly.

4. The breath was held in forced inspiration and in forced expiration. The patients were permitted to breathe between the taking of the different electrocardiographic leads so that the apneic period did not last more than 5 to 15 seconds.

Control electrocardiograms were taken before the experiments, and repeated during the period of overventilation when signs of tetany had appeared and 10 minutes after hyperventilation had ceased. Each tracing was so standardized that corrections for amplitude were not necessary and unimportant.

Fifty-two patients were subjected to 89 experiments; 13 of these patients (as indicated by an asterisk in Tables 2, 3 and 4) were subjected to 3 types of experiments: hyperventilation tetany, rapid and shallow respirations, and forced inspirations and forced expirations. These procedures were done during the same experimental period.

Results. 1. HYPERVENTILATION WITHOUT THE PRODUCTION OF TETANY. Sixteen males and 1 female were subjected to this procedure. Their ages varied between 24 and 46 years (Table 1).

TABLE 1.—THE EFFECT OF HYPERVENTILATION WITHOUT TETANY UPON THE R AND T WAVES OF THE ECG

No. and name	Age	Sex	Diagnosis	CO_2 combining (vols. %)		R waves (mv.)			T waves (mv.)		
				Before	After	Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3
1. R. M.	28	M	Neurosis	64	53	−0.1	+0.05	0	−0.1	−0.1	0
2. C. S.	32	M	URI*	67	60	−0.1	+0.2	+0.25	0	+0.1	+0.1
3. E. D.	45	M	Peptic ulcer	60	52	−0.2	−0.5	+0.15	+0.15	+0.05	0
4. H. H.	35	M	Neuritis	..	..	−0.2	−0.1	+0.15	−0.1	−0.05	+0.15
5. C. M.	46	M	URI	64	53	−0.1	0	+0.15	−0.15	−0.15	0
6. C. T.	34	M	URI	66	58	−0.1	−0.1	0	−0.05	−0.0250	
7. G. C.	40	M	Pulm. tb.	..	..	+0.25	−0.15	−0.1	+0.125	−0.025	−0.1
8. M. G.	46	M	Peptic ulcer	62	52	−0.25	−0.2	+0.1	0	0	I to U
9. M. M.	38	M	Bronchitis	66	56	0	0	0	0	+0.05	+0.05
10. W. O.	43	M	Peptic ulcer	..	..	−0.1	0	+0.1	−0.1	0	+0.1
11. E. G.	28	M	Bronchitis	61	51	−0.2	−0.1	+0.1	0	0	I to +I
12. J. F.	46	M	Neurosis	61	58	−0.05	−0.05	0	0	0	0
13. R. V.	24	M	Parasitic infection	58	45	−0.1	−0.2	−0.1	−0.1	0	+0.05
14. M. S.	37	M	Neurosis	..	..	−0.15	0	+0.15	−0.1	0	+0.1
15. R. S.	30	F	Gastritis	..	..	−0.1	0	+0.1	−0.15	−0.15	0
16. A. A.	24	M	URI	64	55	+0.1	0	−0.1	0	+0.05	+0.05
17. M. S.	38	M	Peptic ulcer	..	..	−0.15	0	+0.15	0	0	0

+ = increase in amplitude; − = decrease in amplitude; 0 = no change; I = inversion of wave; U = uprighting of wave; I to +I = increase in inversion; I to −I = decrease in inversion; D = diphasic.
* Upper respiratory infection.

The R wave in Lead 1 decreased in 15 of the 17 patients. The replacement of an R wave by an S wave did not occur and if an S wave was present it did not become deeper. In 1 patient, the R wave became taller in Lead 1 and in 1 it remained unchanged. In Lead 3, the R wave became taller or the S wave shorter in 10 instances. The R wave became shorter in Lead 3 in 3 patients and 4 times there was no change. Therefore, there was a distinct tendency to right axis deviation. In no instance was there a deviation of the RS–T segment.

The T waves in Lead 1 became lower in 8 cases and in 2 it was higher. The greatest decrease was 0.15 mv. and the greatest increase amounted to 0.125 mv. In Lead 3 an increase in the height of the T wave (or a diminished inversion) occurred 7 times and a decrease of the T wave appeared once. In 7 instances, no changes were registered. In 1 case, the inverted T wave in Lead 3 became upright and in another the inverted T wave became more negative.

Thus in most cases the R and T waves in Lead 1 became smaller while those in Lead 3 became taller.

A study of Table 1 reveals that no correlation existed between the changes in the R waves and the changes in the T waves. At times when the R waves changed their height definitely, the T waves remained unaltered or a lower R wave was followed by a higher T wave.

The carbon dioxide combining power was done in 11 of the patients of this group, before and at the end of the hyperventilation. In all cases there was a shift to the acid side without the production of a true acidosis. Compensatory mechanisms were apparently active which not only corrected the effect of the loss of carbon dioxide but led to a slight overcompensation. Barker obtained similar results.[4]

2. HYPERVENTILATION WITH THE PRODUCTION OF TETANY AND ALKALOSIS. This experiment was done with 35 patients,

12 females and 23 males (Table 2). The ages of the patients varied from 14 to 60 years. The blood pH was determined in the first 10 patients. The values before hyperventilation varied between 7.35 to 7.60 and those after hyperventilation ranged from 7.53 to 7.77.

Twenty-four patients showed a decrease in the amplitude of the R wave in Lead 1 after hyperventilation; an increase was found in 2 instances and 9 subjects showed no change. A decrease of the R wave or a deepening of the S wave occurred 6 times, whereas 13 patients showed an increase of the R wave or a shortening of the S wave in Lead 3. In 16 cases, the QRS complexes remained unchanged in Lead 3.

The T waves in Lead 1 were decreased in 20 instances; no changes occurred in 1 patient and in 14 the T waves became higher. A decrease in the amplitude of the T wave was observed 6 times in Lead 3, an increase occurred in 15 patients and in 14 instances no changes appeared.

Again, the majority of the cases showed a lowering of the R and T waves in Lead 1 while those in Lead 3 became higher.

Figure 1, *A* and *B*, shows the tracings in the 3 limb leads of Patient 7 of Table 2 before and after hyperventilation. There is a significant lowering of the R waves and T waves in Leads 1 and 2 and marked increase of the R waves in Lead 3. Figure 1, *C*, shows the return to the normal picture after 10 minutes. The changes in Figure 1 were the most pronounced obtained in our experiments.

No correlation could be discovered between the shift of the blood pH and the changes in the electrocardiogram. Patients who showed the greatest shift of the pH might exhibit little or no change in the electrocardiogram.

3. Rapid and Shallow Breathing. Very rapid and shallow breathing, averaging 100 respirations per minute, was done

Table 2.—The Effect of Hyperventilation With Tetany Upon the R and T Waves of the Ecg

No. and name	Age	Sex	Diagnosis	Blood Ph.		R. waves (Millivolts)			T waves (Millivolts)		
				Before	After	Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3
1. G. R.*	17	F	Pneumonia	7.39	7.55	−0.05	+0.10	+0.15	0	0	0
2. Y. Y.*	26	F	Nephrosis	7.35	7.53	+0.1	0	0	0	0	0
3. G. W.*	22	F	URI	7.47	7.54	0	0	0	0	0	0
4. S. S.*	28	M	URI	7.48	7.77	−0.05	−0.05	0	−0.10	−0.20	−0.05
5. F. D.*	50	M	Diabetes	7.56	7.70	−0.15	0	+0.15	0	0	0
6. A. B.*	13	M	URI	7.47	7.65	−0.25	+0.30	+0.50	−0.1	−0.2	U to D
7. J. K.*	28	M	Malaria	7.58	7.65	−0.2	−0.1	+0.1	0	−0.02	0
8. V. C.*	18	M	Rheumatism	7.58	7.74	−0.1	0	0	−0.05	−0.05	0
9. T. B.*	41	M	Anemia	7.54	7.71	−0.1	−0.1	0	−0.02	0	0
10. R. C.*	20	M	URI	7.60	7.67	0	0	0	−0.05	0	0
11. J. P.*	25	M	URI	..	..	−0.1	−0.1	0	0	0	0
12. J. S.	14	M	URI	..	..	0	0	0	0	+0.075	+0.075
13. A. S.	37	M	Grippe	..	..	−0.2	+0.1	+0.3	−0.05	−0.1	−0.025
14. M. G.	14	F	Bronchitis	..	..	−0.05	−0.2	−0.15	0	0	0
15. L. O.	29	F	Neurosis	..	..	−0.1	−0.1	0	−0.05	0	+0.05
16. R. P.	28	F	Pleurisy	..	..	0	0	0	0	+0.05	I to −I
17. C. V.	52	M	Peptic ulcer	..	..	0	0	0	−0.05	0	+0.05
18. J. W.	34	M	Bronchitis	..	..	+0.125	0	−0.1	+0.025	0	−0.025
19. A. V.	52	M	Alcoholism	..	..	−0.1	−0.1	0	−0.02	−0.05	−0.025
20. F. M.	47	M	Pulm. tb.	..	..	−0.05	−0.2	−0.15	−0.025	0	+0.05
21. T. H.*	27	M	Malaria	..	..	−0.4	0	+0.4	0	U to I	I to +I
22. A. C.	58	M	G.I. cancer	..	..	0	0	0	−0.025	−0.02	0
23. J. V.	52	M	Peptic ulcer	..	..	−0.025	−0.1	−0.1	0	+0.02	+0.075
24. E. R.	45	F	Neurosis	..	..	−0.1	−0.025	+0.1	0	0	0
25. S. T.	23	F	URI	..	..	0	+0.1	+0.1	0	+0.025	0
26. M. C.	14	F	Bronchitis	..	..	−0.05	0	+0.05	−0.1	−0.1	0
27. Y. N.	23	F	Asthma	..	..	−0.05	−0.15	−0.15	−0.025	0	+0.02
28. R. L.	45	F	Epilepsy	..	..	−0.2	0	+0.2	−0.05	−0.075	I to U
29. H. B.	60	F	Neurosis	..	..	0	0	0	0	0	0
30. S. P.	54	M	Pneumonia	..	..	−0.3	+0.05	+0.25	−0.05	0	+0.05
31. K. G.	55	M	Brain tumor	..	..	−0.15	−0.05	+0.1	−0.05	0	+0.05
32. R. G.	16	M	Pneumonia	..	..	0	0	0	−0.05	−0.05	D to U
33. N. S.	25	M	Pneumonia	..	..	−0.05	0	0	−0.1	−0.15	−0.05
34. E. T.	46	M	Pneumonia	..	..	−0.1	0	+0.1	−0.05	0	+0.05
35. L. K.*	20	M	Atelectasis	..	..	−0.1	−0.15	−0.05	−0.1	−0.1	I to −I

by 11 patients (Table 3). Their ages varied between 13 and 50 years.

The R waves in Lead 1 became lower in 6 instances; in 2 it became higher and in 3 patients it remained unchanged. The R waves in Lead 3 showed an increase in amplitude in 6 patients and in 5 it did not change. Figure 1, *D*, obtained in the same experiment as Figure 1, *A* to *C*, shows that the alterations in the electrocardiogram are the same in both procedures.

The T waves in Lead 1 became smaller in 4 patients and were unchanged in 7. Only in 1 case did the T waves become taller in Lead 3, the other 10 patients showing no change.

4. Forced Inspiration and Forced Expiration. Of 13 patients in this group, 3 were females. Their ages ranged from 13 to 50 years (Table 4).

Forced Inspiration. The R waves in Lead 1 became smaller in 7 instances and showed no change in 4. No increase occurred in the amplitude of the R wave in Lead 1 in 2 patients. The R wave in Lead 3 showed an increase in height in

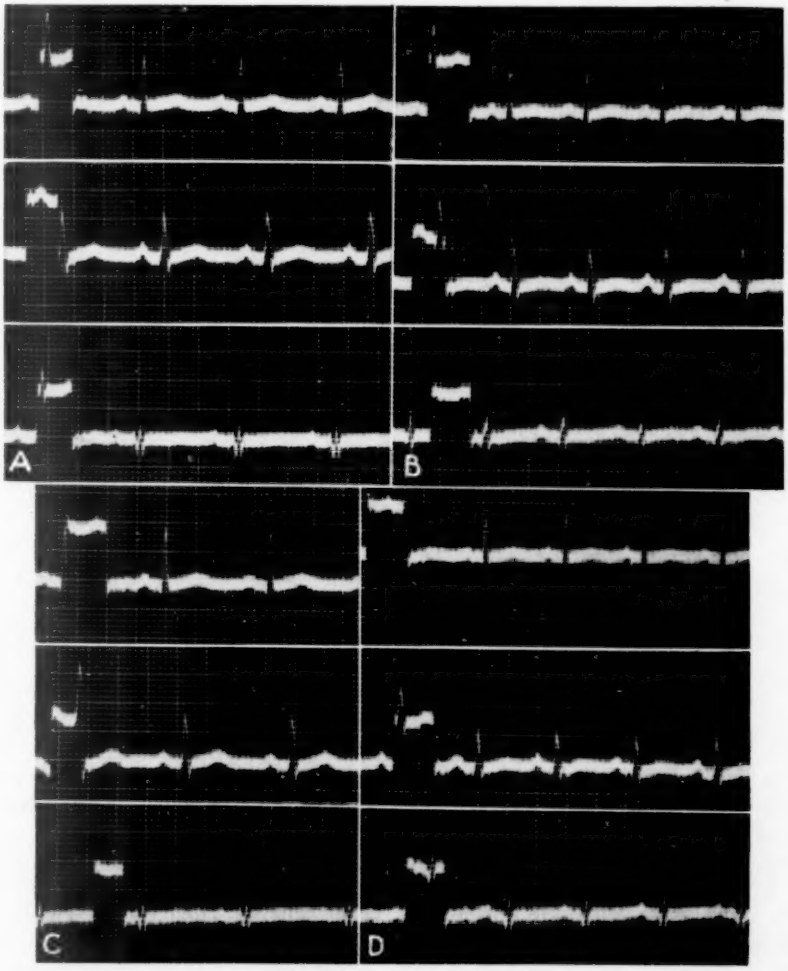

Fig. 1.—Electrocardiogram in standard leads before (*A*) and after (*B*) hyperventilation which caused tetany and alkalosis. *C* shows the electrocardiogram obtained 10 minutes after the hyperventilation. *D* was obtained after 5 minutes of rapid and shallow breathing.

4 patients. Six subjects presented a smaller R wave in the same lead and in 2 they remained unchanged.

The T waves in Lead 1 became smaller in 9 patients and in 2 they remained unchanged. An increase in the height of the T waves in Lead 1 did not occur in any of these patients. In Lead 3 the T waves were taller in 6 patients and remained unchanged in 2 patients. No decrease in amplitude occurred in any of these subjects. In Patient 2 the T wave in Lead 3 became less inverted while in Patient 6 it became more inverted. In Patient 11 the T wave in Lead 3 changed from an inverted wave to an upright one.

Forced Expiration. Four patients responded with a decrease in the amplitude of the R wave in Lead 1, 4 with an increase and in 4 the wave remained unchanged. The R wave in Lead 3 became smaller in 3 records, remained unchanged in 7 and exhibited an increase in amplitude in 2 of the patients.

The T waves in Lead 1 did not change in 9 patients. There was a decrease in height in 3 and an increase did not occur in any. The T waves in Lead 3 remained unchanged in 7 patients and became taller in 2. A decrease in amplitude did not occur. Patient 2 showed an increase in the inversion of the T wave in Lead 3, whereas in Patient 5 the T wave in Lead 3 changed from diphasic to upright. A change from an inverted T wave in Lead 3 to a diphasic wave occurred in Patient 11.

The changes obtained in deep expiration were less extensive than those shown by deep inspiration.

The data obtained in all experiments are summarized in Table 5.

Discussion. From the data presented in the preceding section, one may conclude that smaller changes of the R and T waves were obtained in all 4 series of experiments. These changes were independent of the presence of an alkaline shift in the blood serum and independent

TABLE 3.—THE EFFECT OF RAPID AND SHALLOW BREATHING UPON THE R AND T WAVES OF THE ECG

No. and name	Age	Sex	Diagnosis	R waves (mv.)			T waves (mv.)		
				Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3
1. J. P.*	25	M	URI	−0.1	−0.05	−0.05	0	−0.25	−0.25
2. Y. Y.*	26	F	Nephrosis	+0.1	+0.05	0	0	0	0
3. G. R.*	17	F	Pneumonia	0	+0.05	+0.1	−0.5	+0.5	+0.5
4. G. W.*	22	F	URI	−1.5	−1.0	+0.15	0	−0.5	0
5. F. D.*	50	M	Diabetes	0	0	0	0	+0.5	0
6. A. B.*	13	M	URI	−0.2	−0.1	+0.15	−0.5	0	0
7. S. S.*	28	M	URI	−0.1	0	+0.1	−0.1	−1.5	0
8. J. K.*	28	M	Malaria	−0.1	0	+0.1	−0.5	−0.5	0
9. V. C.*	18	M	Rheumatism	−0.2	+0.15	..	−0.1	−0.05	0
10. T. B.*	41	M	Anemia	0	+0.05	+0.1	0	0	0
11. R. C.*	20	M	URI	+0.1	+0.05	0	0	0	0

TABLE 4.—THE EFFECT OF FORCED INSPIRATION AND EXPIRATION UPON THE R AND T WAVES OF THE ECG

No. and name	Age	Sex	Forced inspiration						Forced expiration					
			R waves (mv.)			T waves (mv.)			R waves (mv.)			T waves (mv.)		
			Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3
1. J. P.*	25	M	−0.25	−0.15	+0.1	−0.15	−0.1	+0.05	0	−0.2	−0.05	0	−0.1	0
2. L. K.*	20	M	−0.25	−0.3	−0.05	−0.2	−0.05	I to −I	−0.15	−0.3	−0.15	−0.05	−0.05	I to +I
3. T. H.*	27	M	..	−0.05	..	..	−0.05	..	..	−0.05	..	0		
4. Y. Y.*	26	F	0	+0.15	0	−0.05	0	+0.05	+0.05	+0.1	+0.05	0	0	0
5. G. R.	17	F	0	+0.15	0	−0.05	+0.025	+0.025	−0.05	+0.1	0	−0.075	+0.05	D to U
6. G. W.*	22	F	−0.075	−0.075	0	0	−0.075	I to +I	+0.1	+0.1	−0.25	0	0	0
7. F. D.*	50	M	−0.20	0	−0.15	0	+0.05	+0.05	+0.05	−0.05	0	0	+0.05	0
8. A. B.*	13	M	−0.35	+0.35	+0.70	−0.075	0	+0.075	−0.1	−0.1	0	0	0	0
9. S. S.*	28	M	−0.15	−0.05	+0.25	−0.15	−0.1	+0.05	0	+0.05	+0.4	−0.05	0	+0.05
10. J. K.*	25	M	..	..	..	..	..	..	+0.15	−0.1	0	0	0	+0.05
11. V. C.*	18	M	−0.075	+0.1	+0.2	−0.1	−0.05	I to U	−0.1	+0.1	0	0	+0.05	I to D
12. T. B.*	41	M	0	+0.1	+0.1	−0.05	0	0	0	+0.05	0	0	0	0
13. R. C.*	20	M	0	−0.1	0	−0.05	0	0	0	0	0	0	0	0

of the signs and symptoms of tetany. The changes were identical whether the hyperventilation consisted of rapid and shallow breathing, rapid and deep breathing, or of slow and deep breathing. The abnormal deviations of the electrocardiogram appeared as early as 3 minutes after the beginning of hyperventilation and returned to normal within 10 minutes after hyperventilation had ceased.

Table 5.—Composite Analysis of the Results

Hyperventilation *without* tetany—17 patients:

R_1	Decreased —15	R_3	Decreased — 3	T_1	Decreased —8	T_3	Decreased —1
	Increased — 1		Increased —10		Increased —2		Increased —7
	No change— 1		No change— 4		No change—7		No change—7
							1 to U —1
							1 to +1 —1

Hyperventilation *with* tetany—35 patients:

R_1	Decreased —24	R_3	Decreased — 6	T_1	Decreased —20	T_3	Decreased — 6
	Increased — 2		Increased —13		Increased —14		Increased —15
	No change— 9		No change—16		No change— 1		No change—14

Rapid and shallow breathing—11 patients:

R_1	Decreased —6	R_3	Decreased —0	T_1	Decreased —4	T_3	Decreased — 0
	Increased —2		Increased —6		Increased —0		Increased — 1
	No change—3		No change—5		No change—7		No change—10

Forced inspiration—13 patients:

R_1	Decreased —7	T_1	Decreased —9	R_3	Decreased —6	T_3	Decreased —0
	Increased —0		Increased —0		Increased —4		Increased —6
	No change—4		No change—2		No change—2		No change—2
							I to −I —1
							I to +I —1
							I to U —1

Forced expiration—13 patients:

R_1	Decreased —4	T_1	Decreased —3	R_3	Decreased —3	T_3	Decreased —0
	Increased —4		Increased —0		Increased —2		Increased —2
	No change—4		No change—9		No change—7		No change—7
							I to +I —1
							D to U —1
							I to D —1

The lack of proportional relationship between the shift of the blood pH to the more alkaline side and the electrocardiographic changes makes the explanation of the electrocardiographic findings by alkalosis unlikely.

Some investigators have found that hyperventilation with hypocapnia causes a marked peripheral and cerebral vasoconstriction.[5,6] Because of these findings, a coronary vasoconstriction with consequent myocardial ischemia has been assumed to explain the changes in the electrocardiogram.[3,16] However, it has been shown that patients placed in a Kettering hypertherm will hyperventilate and show electrocardiographic changes similar to those found in spontaneous hyperventilation.[15] We can safely assume that patients exposed to heat which raises the body temperature to 104° F. do not have a peripheral vasoconstriction. Furthermore it is doubtful that hyperventilation under these conditions will produce an alkalosis. The basal metabolic rate is so much elevated at a temperature of 104° F. that the acid end products of the accelerated tissue metabolism will more than compensate for any loss of carbon dioxide which occurs during hyperventilation.

Finally, it is established that one of the earliest signs of anoxia of the heart muscle is a depression of the RS–T segments in Leads 1 and 2. This is due to the great sensitivity of the inner layers of the myocardium to ischemia. These subendocardial layers are the first to suffer if the blood supply to the heart is diminished. In all of our experiments, a depression of the RS–T segment was absent.

These facts would seem to invalidate both the chemical and vascular changes as a cause for the changes in the electrocardiogram following hyperventilation.

The observation that the inhalation of a mixture containing 5% CO_2 and 95% O_2 will immediately relieve the symptoms of hyperventilation tetany and cause the abnormal electrocardiographic changes to revert to normal,[16] is no proof that the deviations found in the electrocardiogram are due to a loss of CO_2 and consequent gaseous alkalosis. It has been shown that the above gas mixture will cause an increase in the height of the T waves, less inversion of an inverted T wave and the uprighting of a diphasic T wave in cardiac patients without hyperventilation being performed. Patients with normal hearts also showed an increase in the amplitude of the T waves.[2]

The changes in the electrocardiogram caused by hyperventilation with or without tetany and alkalosis were the same as those which appeared when the electrocardiogram was taken during forced inspiration. It has been demonstrated that this positional change of the diaphragm leads to an alteration of the R and T waves which indicates a rotation of the electrical axis to the right.[1,13,18] This change was not obtained in every individual during deep inspiration, for it depends on whether the heart rotates around its longitudinal axis or around an antero-posterior axis, or whether the heart simply moves with the diaphragm without any rotation.

Because of the striking similarity in the changes obtained in all 4 sets of experiments, we feel justified in assuming that the changes produced in hyperventilation were also chiefly caused by a change in diaphragmatic position. It is a well-known fact that overbreathing due to any cause leads to a more inspiratory position of the diaphragm which gradually subsides within a short time after overventilation has ceased.

Lowering of the T waves in Lead 1 also has been observed after exercise in normal individuals with healthy hearts.[19] This has been confirmed in the laboratory of one of us and has been explained by a more inspiratory position of the diaphragm.[11] The lowering of the T waves in Lead 1 after exercise has not rarely been interpreted as being due to coronary artery disease. Exercise as well as any increase in heart rate decrease the ventricular gradient.[1]

Depression of the RS–T segment did not occur in any of our experiments. This is contrary to the experience of other authors who obtained such changes. Only where hyperventilation produced a marked tachycardia did a depression of the RS–T segments in Leads 1 and 2 occur. However, this is a regular finding in tachycardia, whether it is produced by exercise or the administration of atropine or amyl nitrite. This deviation can be attributed to the abnormal depolarization of the inner layers of the myocardium which occurs with an increase in heart rate. The tachycardias obtained by some authors during the hyperventilation was the simple consequence of the physical effort of this procedure.

In some instances the shallow and very rapid breathing may lead to a real anoxia of the myocardium. In this type of breathing the volume of tidal air is reduced to a degree where it surpasses but little the volume of air necessary to fill the dead space, and the exchange of gases suffers.

An inversion of the T waves in Lead 1 did not occur in any of our experiments, although its occurrence in Leads 2 and 3 is common due to a positional change of the heart.[1,13,14,18] The marked immediate T wave changes and the late inversion of the T waves which were observed by Thompson were most probably due to the presence of coronary artery disease, which possibility was even discussed by the author. Hyperventilation in these cases had the same effect as an exercise test. In favor of this belief is the fact that in some patients these abnormally inverted T waves later became temporarily more positive than even the control T waves.[16] This is a well-known after-effect of physical exercise in patients with coronary artery disease.[12] The mechanism involved is similar to that which causes the inver-

sion of the T waves after damage to the external layers of the myocardium (pericarditis) after the elevation of the RS–T segments has subsided.

In recent times even the electrocardiographic changes found in women with the climacteric syndrome and endocrine imbalance were explained by the sighing respiration of these patients, leading to hyperventilation.[16,17] It has been shown, however, that the chief change in these electrocardiograms consists in a depression of the RS–T segments and these changes did not occur in our hyperventilation experiments.

The results of our investigations does not preclude the possibility that under certain conditions T-wave changes are caused by alkalosis.

Summary. The influence of hyperventilation with deep, shallow, rapid and slow breathing on the electrocardiogram was studied. In a majority of the cases, these procedures caused a lowering of the R and of the T waves in Lead 1. These changes are similar to those obtained when the electrocardiogram is taken during maximal deep inspiration.

The alterations of the electrocardiogram are explained by positional changes of the heart. No parallelism has been found between the degree of alkalosis and the changes in the electrocardiogram.

As long as a marked increase in heart rate was avoided and the respirations were not sufficiently rapid and shallow to cause anoxia, no depression of the RS–T segment was observed following hyperventilation.

The alteration of the RS–T segments and the T-wave changes which may be observed in some women with endocrine imbalance is not due to hyperventilation.

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INJECTIONAL TREATMENT OF INTERNAL HEMORRHOIDS

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Just prior to my entry into the Army in November, 1942, I had completed a critical evaluation of injectional therapy for uncomplicated internal hemorrhoids, but postponed its publication for obvious reasons. While in the service I had an opportunity to compare and contrast injectional therapy as practiced in civil life with hemorrhoidectory as practiced in the Army for the same type of lesion.

Material. One hundred consecutive private* patients suffering from uncomplicated small to medium-sized internal bleeding hemorrhoids without or with spontaneously reducible prolapse were treated by submucous and interstitial injections of sclerosing solutions in a manner to be described herein. The follow-up period of study ranged from a maximum of 5 years to a minimum of 6 months; the bulk of the patients was followed for a period of about 30 months. After conclusion of treatments patients were asked to report every 3 months. This program afforded a good opportunity to detect early recurrences. The follow-up examination included a proctoscopic survey in every instance.

A study of the literature as well as personal experience led to the establishment of definite criteria before a patient was accepted for this form of treatment. In all instances it was imperative to establish the absence of active or latent inflammatory disease of the anorectocolonic tube, as well as the absence of concomitant local disease which required surgical excision. Since one of the causes of hemorrhoid formation is congestion with inflammation of the anal structures (anal crypts, anal ducts and anal glands) causing perivascular and vascular involvement, particular attention was paid to this aspect of the problem. Whenever an inflammatory process was thought to be present, it was treated and eliminated prior to the institution of injectional therapy. Experience and the "sixth sense" were helpful in the selection of cases.

Procedure. *A. Preinjectional Studies.* A complete history was obtained and a general physical examination was made. A urinalysis, a hemoglobin estimation and a serologic test for syphilis were performed. The local examination included bidigital and anoproctosigmoidoscopic examinations. Much reliance was placed on the bidigital examination which is performed by the insertion of the index finger into the anal canal and by placing the thumb on the perianal area and gently but systematically palpating the entire anal circumference in a clockwise manner. Localized areas of tenderness which may be missed on routine unidigital examination will invariably be discernible on bidigital examination. These areas of tenderness may represent localized areas of cellulitis, small hidden abscesses, acute thromboses in the deeper anal and perianal tissues or a foreign body. Upon palpating of an involved area or areas the patient usually reacts with a sudden and uncontrolled jerky motion of the body or cries out with pain. The patient remains quiet and cooperative during the examination of the uninvolved areas of the anal canal. In the presence of tender areas, especially when a deep suppuration is suspected, it has been my policy to perform a sedimentation test of the blood. Rapid sinking of the red blood cells, in the absence of other causes, usually indicates the presence of an early hidden perianal abscess.[3] Roent-

* Private cases were chosen for this study because all the details of examination, treatment and follow-up have been carried out by me alone in contrast to clinic patients who are not always treated and supervised by the same surgeon.

gen-ray studies of the colon by means of a double contrast barium enema were made only when specially indicated.

B. Injectional Technique. Most of the patients under study were injected according to a somewhat modified technique described by Lloyd-Davies.[1] The sclerosing agent utilized in most cases was a 5% solution of quinine and urea hydrochloride; 5 to 10% of phenol in pure almond oil was used in a small number of patients. The first injections were made submucously above the anorectal ring about the pedicle of each hemorrhoid with a view to obliterating the hemorrhoidal vein and to fixing the mucosa at a high level in order to prevent prolapse. After all the hemorrhoids have thus been treated, subsequent injections were made into the hemorrhoidal masses at a lower level. Occasionally additional submucous injections were made between treated hemorrhoids in order to correct mild mucosal prolapse. Usually the injections were made biweekly. On occasions all high submucous injections were made in one sitting and subsequent interstitial injections were completed at biweekly or triweekly intervals. A total series of from 6 to 12 injections was required. At present quinine and urea hydrochloride is practically unobtainable. A 5% solution of sodium psylliate (sylnasol) is now employed.

C. Postinjectional Care. The patients were informed that protrusion of the treated hemorrhoidal mass may occur upon straining, especially at defecation. Instructions were issued to avoid straining and how to combat constipation, which may be the cause of defecatory straining. The patients were asked to feel for anal protrusions and were told how to reduce such protrusions digitally and to report such occurrences promptly.

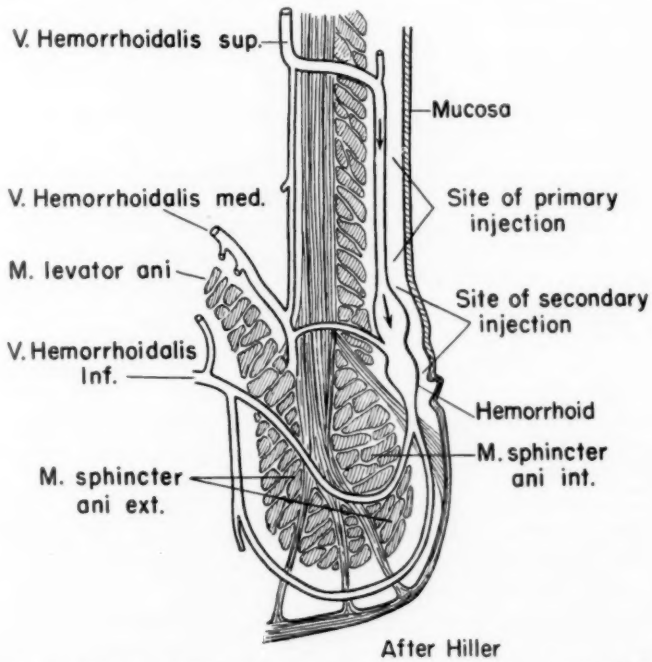

FIG. 1.—Diagram showing the primary and secondary sites of injection. Arrows indicate the reverse flow of blood in the presence of hemorrhoids (Am. J. Surg., **16**, 64, 1932.)

Results. Injectional therapy apparently produces a sterile inflammatory process under the mucosa and within the interstitial tissues of the hemorrhoidal plexus,

causing a chemical thrombosis of the vessels which is followed by sclerosis and finally by fibrosis. The main clinical purpose is to stop bleeding and to correct the associated descensus of the rectal mucosa. This was accomplished in every instance. About 65% of the patients remained symptom-free during a follow-up period of observation ranging from 30 months to 3 years. Reinjection was required in over 30% of the patients because of recurrence of hemorrhoids causing bleeding 9 months or more following the conclusion of the original course of treatment. Injectional therapy apparently does not produce a permanent cure. A cure depends primarily upon (1) the fate of the fibrosis produced which is a biologic unpredictability, and (2) on the elimination of the etiologic factors which had existed prior to the institution of injectional therapy. Since this method of treatment does not remove the original etiologic factors responsible for the development of hemorrhoids, recurrence can hardly be considered a failure in those instances in which the underlying cause has not been eliminated.

Complications. Seven cases of inconsequential superficial slough at the site of injection were observed in this series of patients. This complication was probably the result of leakage of the injected solution through the needle puncture, or the result of injecting too much solution. Other complications (often reported in the literature[2]) such as irreducible prolapse of the treated hemorrhoids into the anal canal or abscess formation, were absent in this series of patients; the absence of the former is attributed largely to the education of the patient and of the latter to the cautious preinjection examination and investigation. Parenthetically, it is my present opinion that suppuration following injectional therapy in many cases is due to an unsuspected or latent inflammatory process which was either overlooked or was impossible of correct diagnosis, rather than to the injections *per se*.

Comment. This study shows that injectional therapy is effective in a large percentage of patients suffering from small to medium-sized internal hemorrhoids without or with spontaneously reducible prolapse. This is an economic office procedure but it is neither simple nor without danger; if the limitations are understood, disappointments and complications will be avoided. The therapeutic success depends to a great extent on the patients' cooperation which can best be secured if the patients are told, in simple terms, something about their lesions and the details of the treatment and if a flat fee is charged. As in the treatment of other diseases requiring multiple injections to be carried out for a given period of time, such a financial arrangement fosters regularity of treatment, confidence, and sincerity of purpose.

To complete this investigation, I felt it desirable to compare and contrast surgical excision with injectional therapy. After treating 6 patients by operation for internal hemorrhoids that I regarded as suitable for injectional therapy, I became so convinced that small and moderate-sized internal bleeding hemorrhoids do not warrant an operative procedure that I discontinued the clinical experiment. However, renewed and ample opportunity to compare and contrast the two procedures was afforded to me while serving in the Army, as soldiers with symptomatic internal hemorrhoids (which in civil practice are considered suitable for injectional therapy) are treated by operation. This added observation and experience confirmed the conclusions of the study of the experimental series of cases in civilian practice, namely, that the majority of cases of symptomatic small or moderate-sized internal hemorrhoids do neither warrant nor require hemorrhoidectomy, with the attendant remote, but potential, risk incident to an anesthetic and a surgical procedure, and the loss of work or duty hours. This is especially true when most, if not all, of these patients can be satis-

factorily treated by the ambulatory injectional method.

Conclusions. On the basis of a study of 100 personally treated and followed patients, it appears that injectional therapy is a safe and effective ambulatory office procedure for the management of the majority of patients with small and medium-sized bleeding hemorrhoids, without or with spontaneously reducible mucosal prolapse, provided that the requirements and details of this therapy as discussed in the text are carried out.

The main purpose of this therapeutic method is to stop bleeding and to correct the associated prolapse which can be accomplished in every instance.

In experienced hands, serious complications can be avoided. The permanence of the therapeutic results is discussed in the text.

Operation is usually not to be applied to the treatment of small or medium-sized internal hemorrhoids, but should be reserved for the treatment of large internal, or interno-external hemorrhoids, and hemorrhoids that are associated with, or complicated by, anorectal lesions that require surgical excision.

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COMPLICATIONS OF MUMPS

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The purpose of this paper is to point out the frequency and variety of complications of mumps seen on the contagious wards of a large general hospital. The material used in this study, obtained from records of Charity Hospital at New Orleans, included all patients with mumps admitted during the period from January 1, 1940, through December 31, 1944.

During this 5-year period, there were 132 males and 82 females, or a total of 214 patients with adequate clinical manifestations for analysis here. Because many patients with mild cases are not admitted to the hospital, statistics from this group may be misleading; however, most of the complications discussed in this paper developed after hospital admission.

Orchitis. Orchitis developed in 28.8% of 132 males in this series, a figure somewhat higher than that usually given in textbooks. Of the 66 who were 15 years of age or older, orchitis developed in 36; only 2 patients under 15 years of age exhibited this complication. Bilateral orchitis occurred in 6 instances; in the remaining cases the right and left testicles were involved an equal number of times. Except for the case herein reported, the course of this complication corresponded to the usual description.

Case Reports. Case 1. A 21-year-old white man was admitted because of fever and a painful, swollen scrotum. Examination revealed a very tender left testicle enlarged to three times its normal size. There was no history of mumps recently, and the etiology of the orchitis was doubtful until 4 days after admission, when the right parotid gland became swollen, as did the mouth of Stenson's duct. Six days later swelling of the left parotid gland was noticed. Recovery was uneventful.

Meningo-encephalitis. Involvement of the central nervous system may occur at any time during the course of mumps, and this complication should always be considered in any patient with encephalitic or meningeal symptoms, particularly during epidemics of mumps. In the present series there were 3 patients with clinical and laboratory evidence of this complication. Others exhibited clinical evidence, but spinal fluid examinations were not done. The following protocols illustrate predominant encephalitic and meningeal forms, respectively.

Case 2. A 9-year-old colored boy complained of headache and vomiting 7 days after the onset of parotitis. During the next 3 days the headaches grew worse, and he became irrational. On admission he was stuporous and lethargic but had no nuchal rigidity or other evidences of meningeal irritation. The spinal fluid was under increased pressure and contained 100 cells, 82% of which were lymphocytes. The symptoms disappeared in about 4 days.

Case 3. A 17-year-old colored girl was admitted, complaining of mild headaches which began 9 days after onset of parotitis. For the next week the headaches became worse and were not relieved by aspirin. She was feverish during this time. On physical examination there was obvious opisthotonos with severe nuchal rigidity. Kernig's and Brudzinski's signs were positive. Examination of the spinal fluid revealed increased pressure, protein 42 mg. per 100 cc. and 600 white blood cells, of which 80% were lymphocytes. With only symptomatic measures, the condition gradually improved during the next 7 days.

Pancreatitis. The incidence and symptomatology of this complication vary widely in different epidemics. One author reported an incidence as high as 15%.[3] In the present series 3 patients with

characteristic symptoms were encountered; 2 of these had only mild manifestations, the most important being a steady, aching pain over the region of the pancreas. The third case is described because of the confusing picture it presented.

CASE 4. A 26-year-old colored man entered the hospital with bilateral swelling of the parotid glands, followed 2 days later by swelling of both testicles. Five days after onset of parotitis, while lying comfortably in bed, the patient suddenly felt severe abdominal pain just above the umbilicus, radiating toward the right side. Examination at this time disclosed an acutely ill patient groaning with pain; there was rigidity of the abdominal wall. A tentative diagnosis of ruptured peptic ulcer was made, and surgical consultation was requested. The leucocyte count was only 6,000, and serum amylase was 180 units. These considerations made the diagnosis of pancreatitis more likely than ruptured peptic ulcer. Conservative treatment was advised, and symptoms gradually subsided over a 2-day period. Except for amenorrhea associated with 2 pregnancies, this patient has had no menstrual irregularities during the 5 years which have lapsed.

CASE 6. An 18-year-old white woman was admitted because of peri-umbilical pain, some nausea, and vomiting. During the day this pain gradually became aggravated and shifted to the right lower quadrant. There was tenderness in this area, with rebound pain over McBurney's point. The white cell count was 7,850. A diagnosis of appendicitis was made, but a normal appendix was found at operation. While the temperature remained elevated and the abdominal pain persisted during the first postoperative day, the left parotid gland became swollen, followed one day later by enlargement of the right one. Fever and abdominal tenderness persisted until the parotid swelling began subsiding. Pelvic examinations during this interval showed tenderness about the right adnexa. An interval of 2 years has elapsed since she contracted mumps, and no menstrual disturbances have occurred.

TABLE I.—INCIDENCE OF COMPLICATIONS OF MUMPS IN 214 PATIENTS AT CHARITY HOSPITAL AT NEW ORLEANS, LA. (1940–1944)

	Number	Percentage
1. Orchitis	38	17.7
2. Meningo-encephalitis	3	1.4
3. Pancreatitis	3	1.4
4. Oophoritis	2	.9
5. Myocarditis	2	.9
6. Edema of the Chest Wall	1	.4
7. Complications of Pregnancy	5	2.3
Total	54	25

The author wishes to express his appreciation to Dr. R. V. Platou, Professor of Pediatrics at Tulane Medical School, for many helpful suggestions in preparing this paper.

Oophoritis. Recognizable involvement of the ovary is a relatively rare complication as compared with orchitis. Symptoms compatible with this diagnosis were present in only 2 of the 82 females in this series.

CASE 5. A 20-year-old white woman entered the hospital complaining of swelling of the jaw and pain in the abdomen. There was no nausea or vomiting. Examination showed, in addition to the parotitis, definite tenderness over both lower abdominal quadrants. The white cell count was 4,000. Abdominal pain and tenderness subsided with disappearance of the parotid swelling.

Myocarditis. This unusual complication was not recognized clinically until recently. In 1944 Wendkos and Noll[2] reported a case; others have since been reported. Two examples have been studied at Charity Hospital. One of these has previously been reported and will not be reviewed here;[1] however, because of its rarity, the second one is presented briefly:

CASE 7. A 6-year-old colored boy was admitted to the pediatric ward for study of backache and low-grade fever of several months' duration. Because rheumatic fever was suspected, an electrocardiogram was made shortly after admission; it was normal,

with a rate of 90 per minute and a PR interval of 0.14 second. The leucocyte count and sedimentation rate were also normal. The hospital course was uneventful until the 16th day after admission, when the temperature became elevated, reaching a peak of 103° F. 3 days later. Examination showed swelling of both parotid glands, typical of mumps. The course of the disease was not unusual, but after 10 days of well-being, the patient had a low-grade fever and appeared less energetic. No cardiac abnormalities were detected, but an electrocardiogram at this time showed a rate of 100 per minute, a PR interval of 0.16 second, and a sharply inverted T4. These indefinite features disappeared in about 10 days, and a subsequent electrocardiogram was normal.

Swelling of the Anterior Chest Wall. Recent literature contains only a few reports of this unusual manifestation. The first case described here occurred during the period of this study; the second case was encountered more recently.

CASE 8. A 7-year-old white girl was admitted to the hospital complaining of swelling of the jaw and pain on swallowing for 24 hours. A sister had been admitted one day previously with a diagnosis of mumps. Physical examination showed bilateral enlargement of the parotid and submaxillary glands. The temperature was 103° F. The white cell count was 6,250, with 55% neutrophils and 45% lymphocytes. On the third hospital day, after the temperature had returned to normal, the swelling spread from the submaxillary region down the neck and extended over the upper anterior thoracic wall. It persisted in the latter area for 4 days, during which time swelling of the neck and submaxillary area disappeared. The white cell count at the time of maximum enlargement was 5,000, with 48% neutrophils. The patient was discharged feeling well 6 days after admission.

CASE 9. A 14-year-old colored boy was admitted to the hospital complaining of swelling of the chest. He had been well until 4 days prior to admission, when he noticed swelling of the left cheek and pain behind the ear, followed one day later by swelling of his neck. On the morning of admission the swelling extended to the chest wall, causing the patient some concern. Seven siblings had mumps at the same time. Examination showed bilateral swelling of submaxillary glands and some enlargement of the upper part of the neck. From the level of the cricoid cartilage downward there was a very noticeable swelling of the soft tissues of the neck anteriorly, extending over the upper part of the sternum to the level of the second rib. Pressure over the involved tissue produced slight pitting, but there was no tenderness. The white cell count at this time was 7,200, with 50% neutrophils and 50% lymphocytes. Four days after admission the presternal edema had completely disappeared. Enlargement of the submaxillary glands gradually subsided during the next week. The patient was afebrile throughout the hospital course, and no other complications occurred.

Mumps During Pregnancy. A search of the literature yielded very little information on this subject; however, the occurrence of clinical mumps in 14 pregnant women out of a total of 82 females justified some consideration of both maternal and progenic aspects. Six of these patients had mumps near or at the time of an uncomplicated delivery, and each of the infants appeared normal. Three other patients had mumps and toxemia of pregnancy at the time of delivery; in each of these, a normal child was delivered, and the neonatal period was uneventful. In 1 the onset of toxemia was definitely related to the appearance of parotitis.

In 2 patients, 7 and 8 months pregnant, respectively, there was onset of labor 2 days after swelling of jaws was noticed. Although delivery and postpartal periods were normal, both babies died. The first weighed 3 pounds 11 ounces, breathed poorly, later became cyanotic, and died 1 day after birth. Autopsy revealed bilateral pulmonary atelectasis in addition to prematurity. The second infant, weighing 4 pounds 13 ounces at birth, lived for 21 days but his condition was always poor, and was characterized by intermittent cyanosis. Autopsy was not performed.

Of the 3 remaining patients, 1 had mumps during the seventh month of preg-

nancy, made an uneventful recovery and delivered at term a normal baby; 5 years later this child appeared to be normal in every respect. The second patient aborted during the fourth month of pregnancy, one week following onset of mumps. In the other patient parotitis developed during the second trimester of pregnancy, and throughout the course of the disease had abdominal pains and cramps justifying an obstetrical diagnosis of threatened abortion.

Summary. The incidence and variety of complications of mumps at Charity Hospital over a 5-year period have been discussed and a brief review of the unusual cases presented. From the data included in Table I, it can be seen that the total incidence of complications is about 25%. It seems unnecessary to emphasize that these complications almost always occur after puberty.

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FURTHER REPORT ON THE USE OF BISMUTH SODIUM TARTRATE INTRAVENOUSLY IN THE TREATMENT OF 203 ADDITIONAL PATIENTS WITH TULAREMIA

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The 203 patients with tularemia recovered following treatment with intravenous injections of a 2% solution of bismuth sodium tartrate. The results obtained in the present series were essentially the same as those in the 61 cases reported[11] previously. Up to June 28, 1946, recovery has ensued in a total of 264 patients with tularemia who have been so treated.

Clinical Observations. The total series included 25 children, 18 adult Negroes and 221 white adults. The absence of any mortality is attributed solely to the fact that treatment was instituted early on a presumptive diagnosis based on the characteristic clinical syndrome and undoubted history of exposure, while awaiting laboratory confirmation. Routine laboratory studies included agglutination tests for tularemia, typhus (*Proteus vulgaris*, O×19), undulant fever, syphilis and typhoid. The serum of 90% of the patients showed positive titers for tularemia of 4+ in 1:360 dilution.

The patients' progress was marked by a routine drop of temperature to 99° F. within an average of 7 days, and all were ambulatory within 18 days. The water-soluble 2% bismuth sodium tartrate solution* was administered in 1 cc. doses daily to all adult patients regardless of sex, age or weight. The dose for children was based on an age-weight basis (an average child of 6 years is given one-half to two-thirds of the adult dose) until the daily maximal temperature remained at or below 99° F., and then every 2nd day until clinical recovery appeared certain. The total number of injections given any one patient varied from 4 to 18. Only 2 instances of gingivitis (all patients were checked constantly by the nurse for this side effect) and 1 of tularemic pneumonia have developed among the total series of 264 patients. The history of the patient with tularemic pneumonia is presented in full in the accompanying case report.

Some of the interesting highlights of the present series of patients were: In the patient with tularemic pneumonia, the house physician thought that bismuth sodium tartrate was life-saving, especially since streptomycin was not immediately available. A Negro patient, with an ulcer on the leg which was believed to be a chancre, a 4+ Wassermann and a temperature of 103° to 104° F., was treated in the accepted manner for syphilis but to no avail. Later tularemia was diagnosed and the patient responded readily to bismuth sodium tartrate therapy. Another patient, with general adenitis, an ulcer on the leg, a leukocyte count of 7000 and a normal temperature, was taking baths at Hot Springs for supposed arthritis, and since no improvement ensued he was referred to us. We suspected tularemia on the strength of the adenitis and the ulcer, both of which promptly disappeared under bismuth treatment. Agglutination tests showed positive titers for tularemia. Because of a similar ulcer and adenitis 34 years ago in this patient's brother, we asked to see him and performed agglutination tests for tularemia; his resulting titer was 3+ in 1:240 dilution. It is believed that the agglutination test remains positive for life, although I have had opportunity to examine the serum of only a few patients 5 years after recovery from tularemia. The serum of each such patient proved positive.

That the serum probably remains positive for life was pointed out by Francis[10a] who stated that the serum of a patient observed by Martin in 1907 showed anti-

* The solution, supplied by G. D. Searle & Co., contains 29.6 mg. of bismuth per cc.

tularense agglutinins in 1925. This observation by Martin in 1907, who encountered several cases of the disease in human beings, was mentioned in a letter which was not unearthed until 1925.

Case Report. The patient, I. W. W., was hospitalized May 21, 1946. He had been ill since May 17. Agglutination for tularemia on admission was 4+ in 1:320 dilution. Intravenous injections of bismuth sodium tartrate (1 cc. daily) were started immediately and continued until May 29, when they were increased to 1.5 cc. and continued to June 4. In addition, 200,000 units of penicillin was given for lymphadenitis of the leg. At this time the temperature ranged from 101° to 105.4° F. A roentgenogram taken May 29 disclosed bronchopneumonia; the patient was placed in an oxygen tent until June 7. He received daily infusions of 1000 cc. of a 10% solution of glucose to which vitamin B complex was added. On June 4 (the 13th hospital day) the patient received 1 gm. of streptomycin; 24 hours later the temperature dropped to normal and after 2 gm. it remained normal except for 1 rise to 99.8° F. He received a total of 5 gm. of streptomycin. On June 14 bismuth sodium tartrate was resumed because of a slight rise in temperature, but it was discontinued on June 17 because of gingivitis. A roentgenogram taken June 18 showed residual bronchopneumonia of the right lung. The patient was discharged a few days later, and is now ambulatory, feeling well, eating well and gaining weight.

Laboratory study on May 22 showed the following: a leukocyte count of 5000; an erythrocyte count of 4,730,000; hemoglobin, 13.2 gm. (79.2%); a color index of 0.8; the sedimentation of leukocytes was 56 mm. in 1 hour by the Westergren method; the unsegmented neutrophils totaled 32, the segmented 41, the lymphocytes 23 and the monocytes 4; the Schilling index was 45+. There was no malaria. Urinalysis revealed an albumin of 2+, a trace of sugar, numerous coarse granular casts and a mixed bacterial flora. Agglutination tests for tularemia were 4+ in 1:320 dilution and typhoid and paratyphoid were cross-agglutinated. Study of the feces was negative as were the Kahn and Kolmer tests. Frequent further laboratory studies showed changes which would normally occur in view of the patient's progress.

Discussion. Despite the favorable results that have been reported recently in a total of 13 patients following the use of streptomycin, the results obtained in my 264 patients would make it appear that bismuth sodium tartrate might be a specific for tularemia. Foshay and Pasternack[10] report that in their 7 patients treated with streptomycin, fever disappeared within 2 to 25 days, the bed period varied from 4 to 28 days and buboes disappeared in 16 to 90 days. Excluding the pneumonia case, the respective figures for our 264 patients were: an average of 7 days for the temperature to drop to and remain at or below 99° F.; the bed period did not exceed 7 days and buboes cleared within an average of 21 days.

Results similar to those reported by Foshay and Pasternack have been obtained by Abel[1] in 3 patients and apparently by Foshay[9] in 2 other patients, as he mentions in this latter article that 9 patients had been treated with streptomycin. Cohen and Lasser[8] report an instance of tularemic pneumonia that did not respond to penicillin and the sulfonamides but in which apparent cure followed the administration of 7,062,000 units of streptomycin.

This makes a total of 13 patients with tularemia who have been treated successfully with streptomycin, but a definitely larger series will have to be had before its efficacy can be proved.

As for other therapeutic agents, in the few patients on whom I have employed penicillin no amelioration of symptoms followed its use and only after resort to bismuth sodium tartrate did recovery ensue. Indeed, it is generally accepted that penicillin has no value in the treatment of tularemia.

Bell and Kahn[3] determined the therapeutic effect of the following preparations on experimental tularemia in guinea pigs: sulfanilamide, sulfadiazine, sulfamerazine, acriflavine, metaphen, iodide and bismuth, arsenic and bismuth, trivalent arsenic,

antimony, penicillin and hyperimmune equine antitularemic serum. Their results demonstrate that with the possible exception of penicillin, none of these agents, given in doses larger than would be used for human beings, showed any therapeutic advantage. Beebe[4] reported a fatal case of tularemic pneumonia after intensive sulfadiazine and penicillin (300,000 units) therapy.

A word of caution as to the transmission of the disease may not be amiss. The term "rabbit fever," although synonymous with tularemia, should be dropped from the medical literature since tularemia is most often caused by tick bites rather than by any of the other numerous possible contacts. In our experience tularemia followed tick bites in 97% of our patients and in only 3% had it occurred after contact with rabbits or squirrels. Pullen and Stuart[15] stress the importance of contacts other than the rabbit. Their list includes rabbits, ticks, squirrels, mink, raccoons, opossums, dogs, cats and rats. These other contacts, they say, are not generally appreciated. Bow and Brown[5] state that the known contacts in 35 of 40 cases of tularemia occurring in Alberta between the years 1931 and 1944 were rabbits, ground squirrels, cats, ticks, grouse, mink, sheep, swine and skunk. In another report Bow and Brown[6] stressed the importance of ticks as contacts by stating that: "Ticks are next in importance to rabbits as a source of infection." However, this has not been found to be true in my practice.

Francis[105] stressed the importance of ticks and tick bites in the transmission of the disease to man. He says in part: "Tick bite, fly bite, and contact with the wild rabbit account for 95% of human cases in the United States." The contacts given by him are wild rabbits, hares, wood ticks, dog ticks, horse flies, sheep, tree squirrels, opossums, sage hens, coyotes, deer, red fox, bull snake, quail, ground hog, muskrat, hog, skunk, cats, Montana ground squirrel, white rats and the water rat.

To this list of vectors the experimental work of Prince and McMahon[14] adds 2 species of tularemia infected fleas: the rat flea, *Xenopsylla cheopis*, and the California ground squirrel flea, *Diamanus montanus*. These fleas produced tularemia in white mice under certain laboratory conditions. These authors cite the work of others who have reported the transmission of the disease, under experimental conditions, by bites of infected flies (*Stomoxys calcitrans* and *Chrysops discalis*), ticks (*Dermacentor andersoni* and *Dermacentor variabilis*), the bedbug (*Cimex lectularius*) and the mosquito (*Aëdes ægypti*).

The muskrat is accused by Williams[17] who reports the first case of tularemia, the ulceroglandular type, diagnosed in Alaska. This patient's illness followed the skinning of numerous muskrats. Williams states that the muskrat as a contact associated with human infections has been reported from Oregon, Idaho, Montana, New York and at Northway on the Upper Tanana River Drainage, Alaska. Bell[2] discusses the nature, incidence and transmission of the infection in ticks. Byfield and his associates[7] review the literature on the transmission of tularemia to man by animals other than the rabbit (mostly ticks) and report 15 cases of their own that occurred in military personnel following tick bites. Their patients were encountered in an evacuation hospital receiving casualties from a maneuver area in Tennessee. There have been a few other recent reports[12,13,16] on tick-borne tularemia.

Conclusion. From a comparison of the results obtained in the 264 patients with tularemia treated by the intravenous administration of bismuth sodium tartrate and the 13 so far reported in the literature who have been treated with streptomycin, it may be concluded that the bismuth treatment has the advantage in that the fever period, hospitalization period and bubo clearance time are all considerably shortened. The mortality was *nil* for our total series of patients. The efficacy of streptomycin in the treatment of tulare-

mia must await further trial, since thus far so few patients have been treated successfully. The bismuth sodium tartrate solution that we use is easily available and in contrast to streptomycin it is inexpensive. Finally, there are fewer possibilities of toxic side effects from bismuth sodium tartrate than from streptomycin, which may at times produce permanent labyrinthine damage with vertigo.

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PROGRESS
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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

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FLEA VERSUS RAT CONTROL IN HUMAN PLAGUE

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The close relationship of communicable disease and military operations has been so long recognized, so decisive in military history, and so stressed in military planning as to be accepted doctrine. An outbreak of mumps has disorganized many a training program. Epidemics of acute upper respiratory infection continue to complicate movements of troops on long journeys. Undue prevalence of even so benign a disease as scabies can interfere with preparations for marshalling an invasion. Dysentery can disrupt a campaign.

The threat of such events is an accepted if not inevitable risk in bringing large groups of men together under conditions associated with military operations. The degree of concern warranted, and the preventive measures deemed applicable, depend upon various factors. The practicability and effectiveness of available control measures are important considerations. The expected gain in health protection or even in health maintenance must be weighed against the inhibiting effect on conduct of normal military activities. The seriousness of a given disease in respect to death and disability may be an issue. A relatively mild condition may attain importance because of the non-effectiveness it engenders.

In developing a general program of prevention, many communicable diseases afford some leeway in procedure or give opportunity for exercise of judgment based on local conditions or the particular military situation. The 5 classical, internationally quarantinable diseases constitute a group permitting little compromise.

Typhus, cholera, plague, smallpox and yellow fever enter more pertinently than ever into military calculations as modern war has become so dominantly global. The reasons are evident and diverse. In the first place, they are capable of wide distribution. Not even yellow fever is a

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strictly tropical disease, as witness the past century entrance of that infection into our northeastern seaports.[3] Cholera has invaded Kentucky.[4] Plague exists in western United States.[11a] Other factors include the ease with which the quarantinable diseases flare into epidemic proportions, the difficulties in control they present, and their universally high case fatality. All at some time have been pandemic, a threat which becomes exaggerated in time of war.

The control of the quarantinable diseases is, of course, no problem peculiar to times of war. It merely becomes more imperative and bears an increased significance. It has always had an important relation to the maintenance of domestic health, as a matter requiring unrelenting diligence. The international quarantine service to guard our seaports against entrance of these diseases was one of the earliest health functions of the Federal government. Air traffic has added to the complexity of this obligation. The current extension of American interests to parts of the world where these diseases are endemic and periodically epidemic increases our concern. The threat of introduction into continental United States will be more frequent. Considerable parts of our population will be resident in plague areas under conditions where American agencies and American physicians must take responsibility for protection against these communicable diseases.

Plague has a special interest at this time. It is one of 3 of the quarantinable diseases which exist within our own territorial borders, recognized endemic foci of infection being present in at least 12 western states.[8] Infection of man has been reported from 9 states,[24] including 3 of the Gulf Coast states, and from the Territory of Hawaii.[7,11b] It has a decided professional interest because of newly developed methods of control offering great promise, but still lacking the experience of extended application which will determine their ultimate value.[13b]

No matter how remote interest and knowledge of plague may be, there is universal appreciation of the epidemiologic principle that the disease spreads along lines of travel. Never in the history of war has an army traveled so far or so widely as did the troops of the United States in the recently completed operations of World War II. Never before has an army been called upon to take up occupational duties in such far-flung parts of the world. No recognized plague area of the world was untouched by American interest and influence, nor unvisited by American soldiers.

The serious plague outbreaks of modern times have been in India, in Burma, and in both south and north China, with Manchuria and Inner Mongolia more or less constant endemic centers.[6b] Plague of the Mediterranean Coast of Africa and the Atlantic Coast of West Africa[1,14,21] has been less extensive but frequent. The consistent presence of plague on the Caribbean Coast of South America[16] and along the Atlantic Coast of Brazil[13a] is less generally appreciated. American military operations, sometimes of major importance and extent, took place in all of these regions during the war.

American troops were stationed also in numerous other areas of recognized lower risk of plague infection, but nevertheless where the disease has been known for many years; where it periodically flares into outbreaks of varying importance; and in many of which it appeared at some time during the war and during tenure of American troops. These include the Azores, certain islands of the West Indies, New Caledonia, Hawaii, and certain western states of the United States.

Not only was the amount and extent of travel by American troops greatly increased during the war, but it was potentially more hazardous travel. Compromise of established measures for international quarantine is unavoidable in time of war. Civilian public health staffs of countries at war are depleted. Necessary supplies for prevention and control of disease among civilian populations are di-

verted in considerable part to military needs. Newly developed methods are at the first disposal of the military. Port control in invaded countries was invariably taken over by the occupying enemy forces; when these areas were liberated, organized port sanitation was commonly found non-existent. Many ordinary regulations and procedures in respect to air and sea traffic were abrogated or modified because of military necessity; others were disregarded through license, ignorance, or exigency. There was a greater potential health risk in international travel during the wa , and greater possibility for spread of the quarantinable diseases.

Despite these adverse features in kind and degree and despite the long residence of United States troops in plague-infected areas, not a single United States soldier contracted plague during the war,[9] and not a single plague-infected rat was found in a United States ship. This was not because of absence of exposure to the disease, nor lack of opportunity for infection. As was anticipated, United States troops encountered plague in both endemic and epidemic degree.

The extent to which plague occurred in areas occupied by United States troops will be outlined in general terms. Continued knowledge of the current world situation was maintained through information from health authorities and medical intelligence arising through military channels. The policy was early adopted, that energetic attack on plague in civilian populations constituted the best means for protecting American troops, through elimination of the disease in the areas where soldiers were compelled to live. There were many such areas. Opportunity was thus provided army medical officers to apply new methods of control made possible by discoveries in allied fields during the war, and to revalue accepted standard procedures.

The greatest plague threat of the war came when United States troops entered north China. This was not a normal north China. The war was over, there was internal disorganization, the country was churned up by many moving populations. Millions of Japanese soldiers had to be evacuated from these areas. Comparable numbers of Japanese civilians had to be removed to their homeland. Hundreds of thousands of Chinese and Koreans were to be returned to their countries of origin from a variety of regions. The potentialities for spread of plague were greatly increased in an area favorable to its transmission and accustomed to its presence. The problem attained no greater significance during the war. Word came to military authorities in southern Korea of the closing of the Manchurian-Korean border by reason of plague to the west. The long separation of that plague endemic area under Japanese occupation had permitted relatively little knowledge of what had transpired in the immediately previous years. A field survey was therefore undertaken to determine the plague situation in north China generally, and particularly in those localities where activities relating to displaced persons and evacuation of prisoners of war would mainly be centered. In preparation for anticipated difficulties, a detailed program of control was formulated. It included the desirable features of standard methods[19,26] and additional measures derived from a variety of experiences with plague in several parts of the world during the war.

Standard Procedures for the Control of Plague. Plague epidemics of man begin as rat epidemics. The first clinically recognized human infections are almost invariably bubonic, arising from the bite of the rat flea. Flea feces containing plague bacilli are rubbed into the minute wound resulting from the insect bite. Depending on environmental conditions, the outbreak may or may not become pneumonic. This form of plague may be a rare event or it may characterize the epidemic. The dominantly septicemic variety of plague is either an overwhelming infection, with death before progress to bubonic or pneumonic types, or a ter-

minal event in bubonic or more commonly pneumonic infection. Plague infection sometimes comes from duties concerned with the care of patients, through discharges from buboes or from the respiratory tract. Not a few accidental infections are contracted by laboratory technicians in the course of examination of pathologic material for diagnosis, or by control workers through contact with infected rodents.

Under any circumstances, the rat occupies the center of the stage. It was, therefore, natural and logical that traditional plague control should be directed against this animal reservoir of the disease. Basic effort has, therefore, consisted in energetic trapping and poisoning of rats, elimination of their breeding places, and curtailment of their food supply.

A second general control measure is quarantine. With this disease perhaps more than any other, quarantine finds its greatest usefulness. It is liberally used. In its point of initial outbreak, plague shows a special predilection for ports, a circumstance intimately related to the density of rat populations in such areas. Strict application of international quarantine is the first consideration among quarantine measures. At times quarantine of whole provinces is indicated, sometimes of cities, or perhaps only of an area within a major concentration of population such as the native quarter. Area quarantine is a measure dating from antiquity. Finally and particularly with pneumonic plague, quarantine and observation of individual contacts is important.

The incubation period of plague is short, a circumstance which gives practicability to these procedures. Through limiting the movements of persons incubating the infection, further contact with the unexposed populations is eliminated. Furthermore, prompt treatment is assured those who become ill, although all too often that is a matter of scant individual profit because of the inordinantly high case fatality.

Specific immunization with plague vaccine is a third general preventive measure. Plague vaccines have been improved in recent years but the protection afforded is still short-lived. Specific protection is an essential adjunct to a control program and should be practiced widely and energetically, but the results to be anticipated are less than in most diseases where such measures are available.

At least 2 sizable outbreaks of plague during the war years were of moment to American troops because of the numbers of men stationed in the areas involved or nearby. The first was in the Yunnan Valley in China, the second involved the Suez district in the Middle East.

Plague in Yunnan, China. The plague outbreak in Yunnan,[6a] southwest China, was by no means the most important in that country during the war years. The province of Fukien was more heavily involved, with an estimated 8279 cases. The adjoining province of Chekiang had 2085 cases. Both areas lie along the China Coast above Hongkong and were happily a problem of the Japanese. The considerable outbreak in Yunnan was of importance to the American army because it lay astride the Burma Road. The Yunnan Valley had been a plague center for many years. The great epidemic of 1894 is believed to have originated there,[10] ultimately spreading to most countries of the world. It was therefore no surprise that plague appeared in 1938 in this general region, in Burma, just beyond the Chinese border. Although reports are indefinite, evidence indicates that the infection smouldered there during the next 2 or 3 years. At any rate, a second small outbreak was reported in 1940 and the same year, the disease appeared on the Chinese side of the border from February to July. A serious outbreak was noted in September and October of 1943 in the Talungchuan region. By 1944 a full-fledged epidemic centered about the general region of Nantien.

Dead rats were found in Nantien in June 1944. One week later the first human infection was noted, a family of 24 being first invaded, of whom 17 contracted the

disease and 9 died. From Nantien the infection spread progressively to nearby villages. December saw a general decrease in reported cases, although plague still continued through January of 1945. Conditions were favorable for spread, in that the whole region was heavily infested with rodents and fleas.

Control measures emphasized principally a rat campaign. Epidemiologic studies arising from this experience indicated available standard measures were applied to all possible advantage permitted by local circumstances in such a region. In the latter stages of the outbreak a large proportion of the population was vaccinated. In Nantien village, 59% of patients with plague were stated to have been immunized previously. Sulfonamides were employed to some extent in treatment of the disease. The generally lower death rate in the Nantien outbreak, as compared with usual experience in this part of China—23 deaths out of a total of 102 cases—is ascribed to these 2 measures. Deaths were most common in the older age groups, among those who had not been immunized, and when treatment was inadequate.

Thus, despite traditional plague control measures under fairly favorable circumstances, the outbreak in the Yunnan Valley smouldered along for 6 years. The disease spread by extension along routes of travel northward. It would appear to have been limited more by exhaustion of susceptibles than any other factor; for example, the village of Nantien with a population of 1000 had 102 cases which, judged by usual experience in China, probably represented no more than a fraction of the actual number.

Plague in Suez. The territory lying along the Suez Canal is a plague area of long standing, though the disease had last been reported in 1932. A few scattered cases occurred in 1939 and apparently an epidemic began to build up from then on, with a few scattered infections occurring each year.[23] In November of 1943, a serious epidemic developed in the city of Suez.[25] From this port city at the south end of the canal, plague spread northward, involving the town of Fayed in February and Ismalia on March 25, although the disease probably had existed before that date. Plague became epidemic in Port Said at the north end of the canal in April. In all, 1581 cases were reported in the area during the winter of 1943–44. Traditional measures of control were employed; a campaign against rats, immunization of troops stationed in the area and to an extent of civilians, and application of quarantine.

These 2 outbreaks in different parts of the world illustrate the difficulties in control of plague by traditional measures of rat control, immunization, and quarantine. That control was not very effective is demonstrated by the length of time the outbreaks persisted, and by their continued progression by extension. Part of the lack of efficiency arises from inadequacies of the measures used. Plague is spread by the rat flea and not by the rat itself, consequently an attack on the rat is at best an indirect measure. On the other hand, lack of accomplishment also arises from the fact that the measures used are often not applied to their maximum. The places where plague occurs are traditionally lacking in trained health workers. There is commonly a lack of responsibility on the part of the population and an unresponsiveness which considers plague one of the inevitable afflictions of life. Supplies and other facilities for satisfactory execution of preventive measures are commonly insufficient. Reporting of all communicable diseases is usually inadequate in the parts of the world where plague is most common, and plague follows the general rule. In China, health officers regard an increase in the number of funerals as the best index of a new epidemic. Consequently an outbreak of plague gains much headway before its existence is realized, and even then rigorous measures may be delayed, sometimes apparently because of the political inexpediency of admitting that the disease

has grown out of hand. Some of these difficulties in plague control are innate and fundamental to the situations under which plague epidemics develop. Improvement in plague control depends in large measure on development of better health organizations. Nevertheless, a simple control measure which would permit direct attack on the flea instead of indirectly against the animal host—a method which is relatively cheap and capable of being applied by workers with little training—would unquestionably be a distinct advance.

DDT in Plague Control. Dakar, and West Africa generally, have a long history of plague. The region is a recognized endemic focus of the disease, and because plague tends to occur periodically, a continuous rat control program was included in the general health program in Dakar for many years. Trapping of rats, use of SO_2 gas in rat burrows, and application of poison in sewers were measures energetically employed from 1934 to 1938. War brought a generally decreased emphasis on rat control, so that during the period 1939 to 1944 little was done. There was general agreement among local observers that the rat population of Dakar had increased appreciably. It was therefore not surprising that plague appeared on April 20, 1944,[20,18] and that typically the first patient was a native occupying a guard hut near the docks in the Arsenal area. Control measures were promptly instituted. Standard port quarantine was established and an active immunization program got under way, in the course of which some 137,000 natives were immunized against plague by use of the single-injection French type of vaccine.

American medical officers introduced a number of measures primarily intended to protect American troops stationed in this region.[12] The waterfront where plague first appeared was placed out of bounds. Native laborers in American military installations were decreased to a minimum. Those still employed were vaccinated and subjected to frequent physical inspection to assure freedom from fleas and to determine developing illness. Later in the outbreak, all employed natives were required to live in a compound in the military area and association with native quarters of the city was prevented. Contact between American soldiers and natives was minimized. American military authorities also for the first time introduced a new measure in the control of plague, in that all quarters occupied by United States troops were dusted with DDT powder, as were all personnel of the United States forces and all employed natives.

The municipal authorities closed all cinemas and discouraged group meetings of any kind. Travel was restricted in and out of the city. Natives were required to carry a sanitary passport showing that they had been immunized and this document was required for the drawing of rations. These measures continued until the epidemic subsided in December. Infected areas within the native quarter were completely quarantined by institution of a *cordon sanitaire* which continued in force until 10 days after the last reported case.

French health authorities had a standard measure for control of plague as it was reported in native areas. The house, yard and general premises where plague had occurred were liberally treated with cresol solution, using a fire truck for gross spraying and the common garden sprinkler for smaller and less accessible areas. The object was to kill fleas and plague bacilli. Fumigation of the "infected" house and sometimes of adjoining houses was carried out with chlorpicrin gas. The house was covered with a tarpaulin, the liquid gas poured on or under the floor and the premises held isolated for 24 hours. The general rat clean-up included adjacent houses. Sulphur dioxide was passed into rat burrows, débris was removed and rats were trapped. Immediate contacts of patients were transferred to an isolation station where their temperatures were taken twice daily. During a part of this experience sulfadiazine was administered in amounts of 20 gm. for adults and 6 gm.

for children over a 3 day period. No factual data are available, but the results of chemoprophylaxis were judged to be good from a limited experience late in the course of the outbreak. Before chemoprophylaxis was instituted, 19 contacts had become ill with plague. After its use only 1 developed the disease. The basic numbers treated were not available.

Despite these measures, plague in Dakar increased during successive weeks of early summer. Eventually, through efforts of United States military authorities, the DDT method of attack which American authorities had been using since the beginning of the epidemic in United States areas and for United States installations, was applied generally as a coöperative effort to all premises where plague had appeared. Houses were dusted with 10% DDT powder. All native residents in the area were likewise dusted.

The area selected for treatment included all territory within a radius of one block of a recognized plague focus, the equivalent of nine square blocks. Later this area was extended in an attempt to anticipate the plague frontier. It became evident, however, that the focal method of attack did not suffice, for plague continued to appear. It was the opinion of American epidemiologists that the areas treated were too limited and that success depended on universal dusting of the whole native area of Dakar, the Medina. Because of disagreement over the necessity for this measure, American authorities withdrew from general plague control activities on Sept. 8, 1945. A continued high incidence of the disease led to subsequent agreement and on October 24 a comprehensive plan to disinsectize the entire native area was undertaken. The work was completed on November 10. As a part of the plan, natives living outside the Medina were provided opportunity for disinsectization on a voluntary basis.

The native quarter was divided into 13 zones. Without notice a cordon of gendarmes was placed around a selected zone at 0500 hours. Four outlet stations in the cordon permitted residents to pass out of the restricted area on their way to work after they were dusted, beginning at 0600 hours. The standard personnel dusting technique was employed and the working population had departed completely dusted within 1 hour. An inner-cordon was then established to isolate individual blocks of the area, and members of the dusting teams went through these areas one by one, dusting all natives who had remained at home, the outer cordon being gradually constricted until all within the prescribed area had been treated. It is estimated that 95% of the inhabitants of a selected zone were so disinsectized. Houses and premises were treated by residual spray or powder. The floor, walls and beds were heavily treated and a lesser dosage applied to the upper walls. In addition to dwellings, all public houses, cafes, restaurants, bars and cinemas were likewise treated. It is estimated that in the course of this work, during which all 13 zones were treated, a total of 125,000 natives were disinsectized with DDT powder. The general program having been completed, fixed stations were maintained in the area, where natives could come for treatment voluntarily in case of reinfestation with vermin.

A major reduction in the flea population of both natives and houses was accomplished. The extent of infestation of houses with fleas of all species, before institution of these measures was determined by first stirring up the fleas through waving the hands, and then exposing a standard piece of fly-paper for 5 minutes. Fleas collected under these conditions sometimes numbered between 200 and 300. Observations after the dusting process showed that houses remained free of fleas for several weeks, the period depending upon dosage applied, the subsequent treatment of the usual sand floors, and the amount of traffic in and out of a given house. Two weeks after completion of the program, 316 houses were visited and only 7 were found to harbor fleas. Under previous circumstances infestation would

have been essentially universal. A second survey on Dec. 8, 1944, showed 33 of 1643 houses to harbor fleas, a proportion of about 2%. It is clearly evident that the method of treatment served to diminish the flea population in remarkable degree. Complete efficiency cannot be attained by such a mass effort. Some houses are invariably missed. Of the 7 houses that had fleas after 2 weeks, the primary dusting had missed 5.

This experience unfortunately does not give a clear evaluation of results to be anticipated from this new method of plague control. The procedure was started late in the epidemic, on Oct. 14, 1944, when reported cases were declining, a seasonal expectation. Nevertheless, the last case of plague was recorded on Nov. 25, 1944, when a native was found dead. It is possible he had been infected prior to completion of the dusting campaign. In any event one accomplishment was wholly definite—the flea population in the native quarter was reduced to almost unbelievably low limits. The outbreak in Dakar was directly concerned with flea-borne transmission, for no patients with pneumonic plague was observed in the course of the outbreak.

Significance of the experiment was increased by the French attitude toward rat extinction. The opinion was held that if rats were killed in appreciable numbers by poison, and the carcasses not recovered, the fleas would leave the rats and go to man as an alternative host. This is in explanation of the standard procedure in rat campaigns in the Dakar area which required that rats be caught alive and drowned in cresol to insure destruction of fleas as well as rats. Because of this policy the number of rats caught and destroyed in Dakar during the course of the outbreak was never very great. This strengthened the presumed accomplishment arising from disinsectization.

The field studies in Dakar were subsequently corroborated by entomologic observations on the lethal action of 5% solution of DDT in kerosene on fleas.[17] When this material was sprayed on floors in concentrations of 100 mg. per square foot, the biting activity of adult fleas was inhibited in 10 minutes. The residual killing effect persisted for 21 days—10% DDT powder applied to floors had essentially the same effect as 5% DDT in kerosene.

Further observations on the control of rat fleas, *Xenopsylla cheopis*, by DDT have been reported.[5] Flea-infested rats treated with DDT powder were not only freed of fleas, but fleas in jars that served as cages were likewise killed. Rats were captured in buildings before and after the building was dusted with DDT. The flea index was 13.9 fleas per rat before dusting; 1 month after dusting it was 0.6; and in 2 instances 0.2 and 0.5 fleas per rat 4 months after dusting.

Chemoprophylaxis of Plague. The suggestive results of chemoprophylaxis in Dakar were extended and given more precise evaluation during a small outbreak of plague in Oran in 1945. This epidemic[20] was part of a general increase in plague along the North African Coast that started in Ferryville in the autumn of 1944. The first patient with plague in Oran was a dock worker who died Jan. 6, 1945, of an illness originally considered influenzal pneumonia, with onset Dec. 29, 1944. Subsequently 8 other natives contracted pneumonic plague, all being close associates of the original dock worker. Spread was by direct contact, and included 2 nurses and a priest attending patients in the hospital. Chemoprophylaxis was employed for 85 direct contacts, maintained under guard during the period of observation and treatment, and given 3 gm. of sulfathiazole daily. Only 1 became ill with plague, and this infection resulted in recovery. The favorable but inconclusive impressions about chemoprophylaxis for bubonic plague in the Dakar experience were confirmed by these satisfactory results with the more serious pneumonic plague in Oran.

Though no rodent plague was ever dem-

onstrated in the Oran outbreak, preventive measures included rodent control. The Dakar experience with DDT was used liberally. Buildings and areas were sprayed with kerosene solution of DDT. Bedding, clothing and persons of natives were treated with DDT powder. Public gatherings were prohibited and areas of infection were placed off limits to soldiers. All members of the U. S. Army were restricted to post during the acute phase of the outbreak. Rat trapping at strategic locations, with examination for plague, was instituted to determine the distribution of plague infection. Segregation of United States from native dock workers was practiced. Troops scheduled for shipment to other ports or areas were isolated for the appropriate incubation period before departure. Re-immunization of military personnel was practiced. Sulfonamide chemoprophylaxis of all inhabitants of heavily infected districts was reserved as an emergency measure. A general conclusion arising from these observations was that larger doses of sulfonamides than those employed were in all probability desirable.

Plague in Casablanca. Plague of both bubonic and septicemic types appeared in Casablanca[2c] on July 20, 1945. As so often happens, the first case involved a French employee in a warehouse of the port area where dead rats had previously been noted. The outbreak was limited to 3 cases, 2 natives and 1 European with no cases among American soldiers stationed in the city.

Control measures instituted by American military authorities included immunization, off limits restrictions except for those recently immunized, and extensive treatment of areas and persons with DDT powder or DDT in kerosene, including warehouses, small buildings, offices, trucks and ships. Strong emphasis was placed on protective clothing. A rat campaign was started. The few cases limited to a single week speaks for the efficiency of these newly developed control measures.

A Modern Program for the Control of Plague. The new insecticide DDT, developed in the course of the war, has brought about a readjustment of attitudes and procedures in the management of epidemics of human plague. Suggestive results achieved in Dakar were further established at Casablanca and by laboratory experiment. The need for a fundamental ecologic attitude[15b] toward the broad problem of plague and its control remains undisturbed. The rat is still the principal reservoir of the human disease. The effectiveness of the new techniques now available serve, however, to establish the principle that attack on the flea is the desirable immediate objective with attention to the rat a long term consideration. Experience in the Oran epidemic enlarged the preliminary observations on chemoprophylaxis as a preventive measure. Results were particularly significant in that the disease was pneumonic plague. This clinical form has a characteristic high case fatality, and attempted interruption of transmission by attack on rodents or fleas is a most indirect approach.

The principles defined as a result of these experiences permit evolution of a more modern program for the control of plague. Three sets of circumstances enter into consideration in respect to the need for plague control and the selection of measures to be applied. The first involves a community with a history of previous plague infection, presumably susceptible to recurrence, but with plague currently absent. The second circumstance pertains to a situation where plague has just appeared, as evidenced by the first sporadic cases. Sound and energetic measures must be brought into play if a widespread epidemic is to be avoided. A third general situation, all too common in areas and populations where plague tends to appear, is of the disease already epidemic or existent in greatly increased proportions; the first report is of an epidemic.

PLAGUE A THREAT. Potential danger of residence in an area frequently plague-infected requires continued attention to

preventive measures and their conscientious practice, even in the absence of known current infections. This applies to all recognized endemic foci.

Vaccination. Irrespective of the practice of native populations, foreigners and military personnel entering endemic areas should be immunized against plague at least 2 weeks in advance of arrival. Initial immunization[2b] consists of 2 subcutaneous injections of plague vaccine, at an interval of 7 to 10 days. The first dose is 0.5 cc. and the second 1 cc. of vaccine.

Protection Against Fleas. Potentiality of an outbreak of plague should be followed by continuing survey of the existing prevalence of rats and rat fleas. An appreciable incidence of fleas, corresponding to a rat-flea index above recognized critical levels, about 0.2, calls for routine protection against the human infestation through use of insecticide DDT louse powder. Weekly use of the powder on underclothing and inner surfaces of shirt and trousers insures freedom from fleas. In military practice, regular physical inspection of men and of quarters for fleas should be required at 2 week intervals.

Rodent Control. Rat surveys of areas suggestive of likely plague infection, and the necessary rat eradication programs[22b] should be instituted by responsible health authorities. In cities, especially port cities, a systematic continuous sampling survey of rats by live trapping will be necessary. The flea index of trapped rats should be noted and rats examined for evidence of plague. Significant increases of rat population emphasize the need for more intensive effort in rodent control. Infected rats determined in the course of routine surveys are indicative of impending plague.

Medical Intelligence. Success in the control of any communicable disease depends on an effective attack in the earliest manifestations of an outbreak. This requires continued and dependable information on prevalence of the disease in the area, and in the case of plague on a system of immediate telegraphic reporting of primary cases. Health authorities of local civilian areas or military installations can accomplish this for their own particular area. It is essential to develop close and frank liaison with health officers of contiguous districts and in areas connected by routes of travel. In military operations, contact must be established with local civilian and military public health authorities to insure early information of plague, even in remote areas with potential opportunity for spread.

Supply. Residence in plague endemic areas requires maintenance of adequate supplies of materials essential to a control program. These include rodenticides, insecticides, flea repellents and plague vaccine. Plague does not always occur in the most accessible parts of the world. Necessary requisition of supplies should not be postponed until plague actually appears, for immediate availability may mark the difference between success in stamping out the disease in its early stages, and the development of an outspoken epidemic.

Training of Personnel. Three special groups of workers are required to carry out modern plague control. Because plague is a disease of uncommon occurrence from a world standpoint, special plague control teams should be organized and instructed in the clinical, epidemiologic,[15a] and diagnostic features[15c] of this disease in advance of known cases. A thorough program of attack should be conceived in advance. Special disinfecting teams are to be instructed in the use of DDT powder and residual sprays, and in measures to be used in disinfestation of persons and premises. The third general need is of laboratory facilities essential to early and certain recognition of the disease. Again, the plague bacillus is not as familiar even to trained bacteriologists as are the agents of diphtheria or tuberculosis. Perfection must be attained in examination of blood, sputum and tissues, and in recognition of rats and rat fleas.

PLAGUE A REALITY. The first appearance of plague should bring into play all

measures available[22a] to eliminate promptly the beginning centers of infection which so often progress so readily to the condition of an outspoken epidemic. The first essential is unequivocal diagnosis. This is a function of experienced epidemiologists in collaboration with laboratories. Primary attention must be directed to patients determined to have plague and to their immediate contacts and environment.

Isolation of Patients. Patients and suspected patients should be kept in separate, finely screened rooms and only authorized and instructed attendants allowed to enter. Attendants of patients with pneumonic or suspected pneumonic infection must wear hoods with goggles or plastic eye-openings, coveralls or complete gowns with trousers, and rubber gloves. All waste articles contaminated by discharges must be burned. Bedding, linens and utensils in contact with the patient should be sterilized by boiling or autoclaving. When a room is vacated the walls, floor and furniture should be disinfected by washing with 5% solution of compound cresol and the room allowed to air for 48 hours. Persons handling bodies of patients who have died of plague should observe strict aseptic precautions.

Quarantine of Contacts. Contacts and suspected contacts of patients with pneumonic plague should be disinfested, segregated and their temperatures taken every 12 hours for 7 days. Those who develop fever should be isolated regardless of the suspected cause. Close contact of segregated persons should be avoided. Inspecting personnel should wear gowns, coveralls and rubber gloves and should be dusted daily with insecticide powder.

Because of the nature of populations usually affected by bubonic plague, the difficulties in controlling their activities, and in assuring proper medical inspection, it is usually advisable that the same measures be employed with this form of the disease as with the pneumonic variety. Precautions in their management need not be as rigid, however, if the area is one in which pneumonic plague is uncommon. In climates where transition from the bubonic to pneumonic type is likely, every precaution should be followed.

Chemoprophylaxis of contacts is strongly urged. Not less than 3 gm. of sulfadiazine should be administered each day for 7 days. This is minimal and may well be increased to the limit of clinical tolerance. Doses as high as 8 gm. per day for the first 3 days have been used for adults. Dosage for children is in proportion to age. The high death rate from plague and the rapid development of the infection require early and intensive application of the method. Vaccination of primary contacts cannot, of course, be expected to yield results because of the time required for production of specific antibodies.

Area Quarantine. Civilian communities where plague is occurring should be proscribed to outside populations until the danger is past. Traffic patrol should be established on roads leading to the infected community to enforce quarantine regulations and to insure that persons entering or leaving the infected area are disinfested with insecticide powder prior to exit or entry. Provisions for such disinfestation should be maintained at road blocks. Control may be made more effective by requiring possession of sanitary passports attesting to vaccination and/or to dusting within a prescribed period. Such sanitary passports can also include the name and address of persons to be visited in the infected area. Definition of the quarantine area depends on the particular epidemiologic situation. It may include only a small restricted area within a city or a district or the entire city. Small villages are treated to advantage as a unit. Within a restricted area, cinemas must be closed and group gatherings and meetings discouraged. The common tendency of inhabitants of a plague infected community to flee to the country or to neighboring villages must be curbed, forcibly if necessary. If refugees are incubating the disease or carrying infected fleas they tend to spread the disease widely.

Foreign Quarantine. Departure from plague areas should require certification that persons are free from plague infection and their clothing and equipment free from vermin. Procedures necessary to permit such assurances should be carried out within 48 hours of departure, including inspection and disinfestation when indicated.

Vessels having contact with ports in plague areas should be protected against entry of rats. This may be accomplished by use of rat-free wharves, by lighterage, or by fending off from wharves a distance of at least 1 meter. Adequate rat guards must be maintained on all lines from vessels to docks or to other vessels and the policing of cargo decks and gang-planks given particular attention. At night, decks and gang-planks should be lighted brilliantly. Steps should be taken to assure that cargo taken on is free from rats. Rat trapping should be continuous on vessels having contact with plague ports, with adequate inspection and fumigation when deemed necessary by quarantine authorities at ports of entry in non-plague areas.

More than the common lip service frequently observed must be enforced under conditions of actual plague risk. This involves as primary requisites a clearly defined, practicable and widely published policy, adequate local supplies and equipment, and above all intelligent, instructed and critical supervisory personnel with adequate authority to enforce their mandates. When military operations are involved, military authority and personnel must supplement the civilian. Generalized platitudes and unkempt waterfront personnel are inadequate when real risk is involved.

Cargo liable to be or actually flea-infested should be assured free from infestation by appropriate insecticidal measures. These may include or consist in storage for adequate periods in flea- and rat-free warehouses. When long voyages are in prospect, intransit time may be taken into account in assuring freedom from fleas when freedom from rodent exposure is assured.

With increased transportation of freight by air many of these precautions must be enforced at airfields. Fortunately, classes of persons most likely to be plague infected or flea-ridden are least likely to travel by air, though exceptions may occur, especially in military or evacuation movements. Effective practicable protection in air as well as in motor traffic demands legitimately elastic enforcement by critically intelligent personnel of applicable effective measures. An uncritical routine may be both onerous and ineffective.

Immunization. Foreign populations and all military populations in plague endemic areas will have been immunized against this disease. They should immediately receive a stimulating dose of 1 cc. of plague vaccine on report of plague in the area. If the outbreak continues this should be repeated every 4 months. Consideration should be given, depending on epidemiologic considerations, to immunizing native populations. This is a desirable part of a long range program though immediate results in decreased incidence cannot be expected. A widespread vaccination program is not the first procedure among personal protective measures. It is very definitely the protection of primary direct contacts by chemoprophylaxis.

Flea Control. The modern control of plague is based on the premise that the flea is the primary objective and that the rat suffering from the disease or harboring fleas is of secondary importance. The principle of focal disinfestation applies.

It is wasteful to attempt to free the universe of fleas, and attack should center about known infected areas, the house or buildings where a plague patient has been discovered. Having described an area within a radius of about 200 yards around the infected house, all persons and infestable things within that area should be disinfested, starting peripherally and working toward the central focus of infection. This is accomplished in respect to persons by dusting every individual with-

in the area with 10% DDT powder.[22c] Pets and domestic animals are treated the same way. Clothing, bedding and furniture within houses are likewise dusted with DDT powder. Walls, ceilings and floors of houses, with especial attention to cracks, are treated with DDT residual sprays in oil. Rat runs and rat harborages are dusted with DDT insecticide powder.

Once the original prescribed focal area has been treated and disinfested, rat trapping lines should be run radially beyond the focal zone. If plague infected rats or rats with high flea indices are discovered, disinfestation should be extended, again proceeding inward from the outermost point of suspected infection.

Depending on the degree of success attained with focal attack, the extent to which plague is present in various parts of the area, and the general trend of incidence, consideration should be given to disinfesting methodically all parts of the affected section of the city or district. This is best accomplished by defining grids or sections of the general area, establishing police cordons, and methodically treating with DDT all persons and susceptible things within the area. It is invariably wise to start with the focal method of attack. This may be enlarged either by extension of the original focal area, or on a general community basis.

Foreign residents within or adjacent to a plague infected area should be disinfested weekly with 10% DDT powder, applied by hand or power duster.

Hospitals, barracks, mess halls and store rooms of military installations and the quarters, clubs, stores and common meeting places of foreign residents, within or adjacent to a plague infected area should be kept free of fleas by use of DDT powder or residual sprays. Rat harborages should receive special attention.

Protection of Personnel Engaged in Plague Control. Personnel engaged in plague control should apply insect repellent to exposed skin in the manner prescribed for protection against mosquitoes. While repellents do not prevent fleas from lighting, the insects nevertheless tend to leave the treated surface almost immediately and do not bite. Clothing, including socks, should be impregnated as with dimethylphthalate. All personnel should be required to wear trousers tucked into boots or leggings, and shirts with long sleeves.

Rodent Control. When human plague is discovered, the extent of the disease among the rodent population should be determined by trapping in every direction from the determined focus of infection until no additional infected animals are found. Destruction of harborages, rat-proofing and rat extermination should be carried out subsequent to focal disinfection, by working again from the periphery towards the center of infection. All buildings and ships should be rat-proofed. Rat extermination should include trapping, the use of poison, and fumigation. Finally, attention should be given to garbage collection and disposal, to removal of trash piles and to protection of foods as measures to decrease the rat population, and thereby the flea population.

Natives Employed on Military Posts or Within Foreign Compounds. Natives from a town or village where cases of plague are occurring should not be admitted within army unit areas or foreign compounds. The number of natives employed within such areas should be reduced to a minimum, and they should be required to live on the post or within the compound. If this is impractical, they and their quarters should be disinfested and each employee examined twice daily for fever or other evidence of plague.

Plague in Epidemic Proportions. Measures indicated when plague is epidemic do not differ in kind from those required in the management of the first sporadic cases. The need is for intensified effort with expanded manpower and supplies. Ordinarily the special teams designed and available for epidemiologic studies and for disinfestation are inadequate for the needs of a true epidemic. More teams must be organized. They

need not be experts, for much can be accomplished, particularly in disinfestation, by quickly trained men. Given brief but intensive instruction, case finding teams can be enlisted from ordinarily available medical personnel. The training may be by the regularly constituted organizations.

Operation of Case Finding Teams. Case finding teams are employed for epidemiologic case studies of all reported instances of plague or suspected plague, with special attention to sources of infection and identification of contacts. They initiate preliminary and emergency control measures for each suspected or confirmed case of plague, including removal of the patient to hospital, and disinfestation of the patient, immediate contacts, and the patient's immediate environment. The principal effort in case finding lies in organized house-to-house search for unrecognized cases within the infected community. It is to be stressed that the knowledge of civilian living habits and of the language are helpful.

Case finding teams will make use of numerous unskilled civilian personnel in the conduct of their activities. They need to assure that immunization and disinfestation of these workers is practiced regularly.

The operation of isolation hospitals in the kind of communities where plague occurs often leaves much to be desired. Through uncontrolled visiting of relatives or other inadequate control, contacts can be multiplied and extension of the disease into new communities facilitated rather than hindered by an improperly managed isolation hospital. It is the duty of case finding teams to consult and aid in the provision of adequate isolation measures.

Operation of Disinfestation and Rodent Control Teams. Local disinfestation is a primary function of disinfestation and rodent control teams. In the area immediately surrounding cases, surveys are made of rodent and flea populations, with the subsequent obligation of flea and rat extermination in infected communities and in nearby uninfected areas. Dusting facilities in quarantine control in ports are likewise a responsibility of the disinfestation teams.

Cordon Sanitaire. An emergency measure to be instituted only after careful consideration is the *cordon sanitaire*, by which areas of plague infected territory are marked off from larger relatively remote uninfected areas. It is ordinarily without benefit to attempt this measure under other than the prescribed conditions. Furthermore, a strong natural barrier between infected and uninfected areas is requisite to satisfactory protection and guarding of a *cordon sanitaire*, such as a range of mountains or a fairly impassable river.

Summary. The first consideration in control of human plague is direct attack on reported foci of infection. This involves (1) diagnosis and recognition of the disease, which is essential to establish firmly the existence of plague, (2) isolation of the patient and of the immediate contacts, proper treatment of the patient and protection of contacts by chemoprophylaxis, and (3) focal attack on the area invaded by plague, through disinfestation of premises and persons with insecticide DDT.

Further definition of cases and sources of infection through case-finding and the application of area and foreign quarantine follow in order.

General measures for limiting the spread of the infection are to be established promptly. These include the practice of immunization and re-immunization, management of remote contacts, relations with native populations, measures for personal protection of foreign and military populations and rat campaigns.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF JANUARY 15, 1947

Light and Dark Adaptation of Single Visual Sense Cells. H. K. HARTLINE, M.D., and R. MCDONALD, M.D. (Johnson Research Foundation and Dept. of Ophthalmology, Univ. of Penna.). Changes in sensitivity of visual sense cells in the eye of Limulus during dark adaptation have been followed by recording the impulses discharged in single optic nerve fibers in response to test flashes of light. Following exposure to light the number of impulses discharged in response to the test flash is less than the number elicited by this same flash when the sense cell is completely dark-adapted. Recovery of sensitivity during dark-adaptation is rapid initially and approaches the dark-adapted value asymptotically. The higher the intensity and the longer the duration of the preceding adapting exposure, the greater is the initial reduction in sensitivity of the receptor, and the slower the recovery. Recovery following prolonged illumination at low intensity is slower than recovery following a short, bright flash, even though the initial reduction in sensitivity is the same in both cases. These results can be explained qualitatively by visual cycle of photolysis and regeneration such as that proposed by Wald.

The frequency of discharge in the response to a test flash is much less affected by light and dark adaptation than is the total number of impulses. Thus it is not possible to match responses obtained under different conditions of adaptation merely by altering the intensity of the test flash until the number of impulses is equal. During light and dark adaptation, therefore, other changes must take place in the visual sense cell than simple alterations in sensitivity due to altered concentration of photosensitive substances.

Oxygen Consumption of the Cerebral Cortex During Metrazol Convulsions in Cats. P. W. DAVIES, PH.D., and ANTOINE RÉMOND, M.D. (Johnson Research Foundation, Univ. of Penna.). These experiments were performed with the aid of microelectrodes which measure oxygen tension locally by direct electrolytic reduction of dissolved oxygen (Davies, P. W., and Brink, F.: *Rev. Sci. Instr.*, **13**, 524, 1942). The cats were paralyzed with intocostrin to prevent convulsive movements, and were given repeated doses of metrazol resulting in periodic convulsions of status epilepticus, as indicated by electrocorticograms from the experimental area.

One line of evidence regarding oxygen consumption was obtained by following oxygen tensions at the cortical surface. An extremely flexible electrode less than 75 microns in diameter allowed such measurements to be made without movement artefacts. It was found that both venous and tissue-space oxygen tensions declined just after the appearance of the extra electrical activity of a seizure, rising again during the period of extinction. The arterial oxygen tension remained constant throughout. Since cerebral blood flow increases during a seizure, these results can be interpreted only by assuming an increased cortical oxygen consumption following increased nerve cell activity.

A second line of evidence was obtained from direct measurements of local oxygen consumption. This was done by causing sudden local occlusion of the circulation of the cortex and measuring the subsequent rate of fall of oxygen tension of the occluded region. A rigid oxygen cathode mounted on a movable arm, allowing it to be pressed against the brain, served both to accomplish the occlusion and to meas-

ure oxygen tension. By repeating the process a fairly continuous record of metabolism was obtained. In this way, it was found again, that cortical oxygen consumption increases after, rather than before, the increased electrical activity. The maximum rate is about double the initial, which agrees with the findings of Schmidt, Kety and Pennes (*Am. J. Physiol.*, **143**, 33, 1945), and is only reached toward the end of the seizure. During the quiet phase consumption gradually returns to normal over a period of a minute or so.

Kidney Phosphatase in Alimentary Hyperglycemia and Phlorhizin Glycosuria. A Dynamic Mechanism for Renal Threshold for Glucose. By JULIAN B. MARSH, A.B., and DAVID L. DRABKIN, A.B., M.D. (Dept. of Physiological Chemistry, School of Medicine and Grad. School of Medicine, Univ. of Penna.). The enzymatic rôle of kidney phosphatase in the reabsorption of glucose in the renal tubules was studied under the conditions of alimentary hyperglycemia and phlorhizin glycosuria. Employing the homogenization technique in a modified method for the measurement of phosphatase activity a 55 to 70% increase in the activity of kidney acid and alkaline phosphatase was found after 2 hours in rats given 1 to 3 gm. of glucose by stomach tube.

Previous *in vitro* studies of the inhibitory effect of phlorhizin on kidney acid phosphatase activity were confirmed (Beck, L. V.: *Proc. Soc. Exp. Biol. and Med.*, **49**, 435, 1942). The alkaline phosphatase activity was also found to be inhibited, 0.01 M phlorhizin producing an inhibition of 40% in acid and 91% in alkaline phosphatase activity. For the first time, an effect of phlorhizin on kidney phosphatase was obtained *in vivo*. Using very concentrated homogenates of the kidneys of rats injected subcutaneously with 140 mg. per kg. of phlorhizin in oil, it was shown that the acid and alkaline phosphatase activities of these phlorhizinized rats' kidneys were 41% lower than the activities of similar homogenates from normal controls.

Studies on some components of the phosphorylating enzyme system in the kidney were made in the alimentary hyperglycemic state. The ATP content proved to be of the same magnitude in the kidney tissue from fasted and hyperglycemic rats. Using the technique of Colowick, Welch and Cori, an inhibitory effect upon phosphorylation and oxygen consumption owing to increased dephosphorylation was demonstrated in experiments in which phosphatase activity was increased by means of the addition of a preparation of the enzyme to kidney homogenates (Colowick, S. P., Welch, M. S., and Cori, C. F.: *J. Biol. Chem.*, **133**, 359, 1940).

As a consequence of these findings, it was postulated that the phenomenon of renal threshold for glucose is at least in part an expression of the limit to which kidney phosphatase can be raised.

Cerebral Blood Flow and Metabolism in Patients With Severe Diabetic Acidosis or Coma. SEYMOUR S. KETY, M.D., B. DAVID POLIS, M.S., CARL S. NADLER, M.D., and CARL F. SCHMIDT, M.D. (Dept. of Pharmacology, Univ. of Penna., and Metabolic Service, Phila. Gen. Hosp.). During the past year 13 patients admitted to the Metabolic Service of the Philadelphia General Hospital in severe diabetic acidosis or coma have been studied from the point of view of cerebral blood flow and metabolism in an effort better to define the biochemical and physiologic derangements which occur in this disease. The group consisted of 7 males and 6 females; the average age was 43. The mean for blood glucose concentration was 560 mg. %, for arterial CO_2 content 12 vol. %, for pH 7.06. Seven patients recovered and were ultimately discharged from the hospital; the remaining 6 died within 24 hours of admission. These 2 groups do not differ significantly with respect to age, pH, CO_2, glucose, blood electrolyte patterns or cerebral blood flow

on admission. The group which ultimately recovered, however, exhibited lower blood ketone concentrations, higher blood pressure, better mental status and higher cerebral oxygen consumption at the time of the initial studies. Cerebral oxygen consumption appears to have considerable prognostic value and there is evidence for a critical level of cerebral metabolic activity, values below this being incompatible with recovery.

Cerebral blood flow is not significantly different from normal and is not correlated with recovery. This argues against circulatory failure as an immediate cause of the disturbances in cerebral function. Cerebral blood flow is well correlated with arterial pH as is also respiratory minute volume. These correlations in the face of extremely low CO_2 tensions in arterial blood speak for hydrion concentration rather than CO_2 as an important mediator of these functions in this condition.

Cerebral metabolic rate (measured as cc. of O_2 utilized per 100 gm. of brain per minute) is well correlated with mental state in these patients. It is not correlated with either cerebral blood flow or arterial pH, thus indicating that cerebral depression in this condition is caused neither by decreased blood flow nor acidosis. There is a good correlation, however, between decreasing cerebral metabolism and ketosis in these patients before and after treatment. Further studies may show a causal relationship here or elucidate an even more fundamental mechanism upon which both are dependent.

BOOK REVIEWS AND NOTICES

CURARE INTOCOSTRIN. Unsigned Abstracts with Introduction by H. SIDNEY NEWCOMER, M.D., Medical Director of E. R. Squibb & Sons. Pp. 292. New York: E. R. Squibb, 1946.

THIS book aims to acquaint the medical profession with the many new and important clinical possibilities of intocostrin, a physiologically standardized curare preparation. It is a compilation from scientific contribution concerning intocostrin and other curariform drugs. The book is arranged in 2 sections: the first section is devoted to papers concerning history, pharmacology and chemistry, the second to those concerning the use of intocostrin in anesthesia; shock therapy; spasticity, rigidity and tremor; poliomyelitis; endoscopy; tetanus convulsions; and the diagnosis of myasthenia gravis. An author index and a subject index provide concise reference to the recent literature on the subject of curare. This book accomplishes its purpose in serving to facilitate the study of those interested in the pharmacology and chemistry of curare and in making available the essential knowledge thus far obtained on its therapeutic uses. C. L.

A HISTORY OF MEDICINE. By DOUGLAS GUTHRIE, M.D., F.R.C.S. (EDIN.), F.R.S.E. With an Introduction by SAMUEL C. HARVEY, M.D., F.A.C.S. Pp. 449; 78 plates. Philadelphia: Lippincott, 1946. Price, $5.00.

THE Preface to Osler's Silliman Lectures delivered at Yale University in 1913 on "The Evolution of Modern Medicine" contains a quotation from a letter written by Sir William to one of the editors in which he describes these Lectures "as an aeroplane flight over the progress of medicine through the ages," a description which could very aptly be ascribed to Dr. Guthrie's charming volume. As he states in his Preface he has attempted to "construct an outline of the progress of medicine from the days of Imhotep to those of Sir Willam Osler. An outline does not aim at finality, and many worthy names have been omitted in order that the story may not interest by being overweighted with details." We think he has succeeded in his aim. This book recalls to mind that of Withington, which Osler admired so much, "Medical History from the Earliest Times." Beginning with a brief yet sufficient outline of prehistoric medicine, Guthrie continues with chapters on the medicine of the Egyptians, Greeks, Romans and Arabians, and the Medieval and Renaissance periods. Scientific medicine really began with Vesalius, and went through a long labor in which it was assisted by Harvey and the microscopists von Leeuwenhoek, Swammerdam, Hooke, and the anatomists de la Boe, Ruysch, Willis, Glisson and many others. As might be expected Guthrie is particularly to be commended for his story of the development of medical science in Scotland under the Monros, Cullen, and of the continuance of their work in London by their fellow-countrymen, the Hunters. There were giants in surgery in the early 18th and 19th centuries both in Great Britain and on the Continent, particularly in France. In London, Astley Cooper, Brodie and Abernethy; in France, Larrey and Dupuytren were great surgeons, and in Paris, Laennec, Corvisart and Bichat drew pupils from all over the world.

In the middle of the century Clio Medica moved to Germany and, until the beginning of the World War I, men like Koch, Virchow, Ehrlich and others were the great leaders. In the middle of the 19th century Pasteur in France was easily the greatest medical scientist of his day, and Lister in England the foremost scientific surgeon. Guthrie devotes adequate chapters to military and naval surgery and the conquest of tropical diseases; the rise of specialism and preventive medicine, and concludes with an excellent chapter on medical journalism, bibliography and medical history. Each chapter is furnished with adequate notes and references and at the conclusion of the book there is a classified bibliography of medical history and an excellent index. There are a few errors in the book, such as making William Penn, who died in 1718, a friend and con-

temporary of Dr. John Fothergill, who was born in 1712. It was Thomas Penn who was Fothergill's contemporary and friend.

The illustrations are notable, well chosen and reproduced. Dr. Guthrie's book deserves a warm welcome from all those who are interested in the subject. Though not a work of reference, such as Garrison's or Castiglioni's, it covers the most important subjects in medical history from the earliest times to the present day in a most interesting manner, omitting little of real importance.

F. P.

PNEUMOPERITONEUM TREATMENT. By ANDREW LADISLAUS BANYAI, M.D., F.A.C.P., F.C.C.P., Associate Clinical Professor of Medicine, Marquette University Medical School, Milwaukee, Wis., Member, Editorial Board, "Diseases of the Chest;" formerly Preceptor in Tuberculosis, School of Medicine, University of Wisconsin, Madison, Wis. Pp. 376; 74 ills.; 16 tables. St. Louis: C. V. Mosby, 1946. Price, $6.50.

THE author has gathered in compact and orderly form his observations and experiences in the use of artificial pneumoperitoneum since 1931. The book includes useful information on technique and the physiologic and anatomic changes in the peritoneum during treatment. Complications such as air embolism, accidental pneumothorax, mediastinal emphysema, subcutaneous and periperitoneal emphysema, pneumocele, urinary retention, cardiac decompensation and unusual digestive symptoms are discussed. The 2nd section of the book takes up specifically the treatment of tuberculous peritonitis, tuberculous enterocolitis and pulmonary tuberculosis with artificial pneumoperitoneum. The last 48 pages discuss numerous other applications of pneumoperitoneum such as treatment of tuberculous emphysema, tuberculous salpingitis, pulmonary abscess and bronchial asthma. Dr. Banyai is conservative and takes great pains to place artificial pneumoperitoneum treatment in its proper position among all measures in the treatment of tuberculosis. The text is supplemented by numerous reproductions of Roentgen ray films which are adequate to show the results obtained, although not of the highest quality. This book should be a useful addition to the library of any clinician who treats tuberculosis.

H. C.

UROLOGIC ROENTGENOLOGY. By MILEY B. WESSON. 2nd ed. Pp. 259; 258 ills. Philadelphia: Lea & Febiger, 1946. Price, $5.50.

THIS edition of an already popular book contains a larger number of excellent illustrations. The text has been kept brief yet fairly comprehensive. The book was originally written for those learning to interpret urograms, but many of the illustrated cases will be of interest to those with wider experience.

The technique of combined urography with ureteral catheterization, described by the author, will not and should not be used by those not trained in cystoscopic work. Nor should it be used when demonstration of the physiology of the urinary system is desired.

Despite published reports of pitressin "reactions" the author continues to advocate its use in the preparation of patients for excretory urography.

These minor criticisms should in no way detract from the overall value of the book, for it remains a valuable addition to the library of the student of urography.

C. P.

PEPTIC ULCER. By I. W. HELD, M.D., F.A.C.P., Consulting Physician, Beth Israel Hospital, formerly Clinical Professor of Medicine, New York University, College of Medicine; and A. ALLEN GOLDBLOOM, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, New York Medical College and Flower-Fifth Avenue Hospital. Pp. 382; 110 ills. Springfield, Ill.: C. C Thomas, 1946. Price, $6.50.

THIS pleasingly printed and bound volume represents a wide personal experience with peptic ulcer and its complications. Well-organized with chapters on all phases of the problem, from pathogenesis to postoperative management, the text is profusely illustrated and easy to read. Considerable attention has been given to differential as well as to pathologic and roentgenologic diagnoses. The rarer types of peptic ulceration as found in the esophagus, Meckel's diverticulum and in childhood are discussed in detail. Numerous references are given, particularly to the German literature, and on controversial subjects the authors have summarized the divergent opinions. They have omitted from their discussion on treat-

ment, however, many of the recent American reports on such subjects as vagotomy for recurrent ulcer and the early feeding regimen for gastro-intestinal bleeding. Likewise no mention is made of the spot film technique in the section on roentgenologic diagnosis or of the work on effects of hormones on gastric function. Many will disagree with the emphasis placed on recurrent appendicitis as a factor in ulcer symptomatology and gastric hemorrhage. This book may be read with profit but cannot be regarded as an all-inclusive text. J. N.

DOCTORS EAST, DOCTORS WEST. An American Physician's Life in China. By EDWARD H. HUME, M.D. Pp. 278; ills. New York: W. W. Norton, 1946. Price, $3.00.

DR. HUME, the only American physician at the time in Bombay, accepted a call to China in 1905 "to launch a university medical school" (Yale-in-China). This book records, entertainingly, his life there "at a time when Westerns were beginning to try to understand Chinese medical thought, and when China was beginning to recognize the need of the western approach to scientific medicine." The narrative of the author's life at Changsha gives a good picture of the modern medical missionary's work in his effort to build cultural bridges between nations of widely different histories and points of view. The author eventually retired from the Yale School, so as to turn over leadership to Chinese administrators; but, returning on a visit years later, he found "a good harvest." The famous treks to Kweiyang and 6 years later to Chungking are described in a short epilogue. E. K.

STROPHANTHIN. Clinical and Experimental Experiences of the Past 25 Years. By BRUNO KISCH, M.D., formerly Professor on the Medical Faculty of Cologne University (Germany). Pp. 158; 24 figs. New York: Brooklyn Medical Press, 1944. Price, $4.00.

THIS monograph was written for the express purpose of acquainting American physicians with the continental attitude toward strophanthin therapy in the hope of influencing them to use intravenous strophanthin in place of digitalis. Cardiologists and other internists will find in this book a review of the literature, chiefly German, and a 29 page bibliography dealing with the pharmacology and clinical usage of the cardiac glucosides. American physicians have long been aware of the fact that intravenous strophanthin produces its effects much more rapidly than do digitalis preparations taken orally, and that consequently strophanthin is to be preferred in emergency cases of severe congestive heart failure. American physicians have long believed that oral medication, when effective, is far superior to parenteral injections for the treatment of chronic diseases. Some physicians consequently will be annoyed by the author's insistence upon the superior virtues of strophanthin, especially since no new or noteworthy experimental evidence is presented.

It is true that powdered digitalis is not completely absorbed from the gastro-intestinal tract. Ideally, however, digitalis is not given in fixed doses but in amounts which produce certain definite effects upon the patient. One hesitates to recommend routine intravenous therapy, with strophanthin, digitalis or any other drug unless all other routes have been tried unsuccessfully.

Cardiologists will be interested in many portions of this monograph, especially those reviewing foreign literature not widely quoted in this country. J. C., JR.

DISORDERS OF THE BLOOD. By SIR LIONEL E. H. WHITBY, Regius Professor of Physics in the University of Cambridge, and C. J. C. BRITTON, Assistant Pathologist in the Bland-Sutton Institute of Pathology, Middelsex Hospital. 5th ed. Pp. 665; 71 ills. and 15 plates. Philadelphia: Blakiston, 1946. Price, $10.00.

THIS edition brings the literature up to early 1945. As in previous editions, it is a well-written and clearly worded textbook for students of hematology. Since the first edition in 1935, an outstanding feature has been the addition of a summary at the end of each chapter. The following subjects have been revised since 1942: origin and development of blood cells, hemolytic anemias, anemias of infancy and childhood, hemagglutination, and blood transfusion and technique. Other subjects have been brought up to date, but apparently the book went to press before the advent of folic acid and

there is no mention of the work of Winsor and Burch on sickle cell anemia. There is a laudatory attempt to simplify and clarify the nomenclature but it continues to be somewhat confusing—a fault of the science, not of the authors. The authors continue to emphasize that changes in the blood are most often secondary to disease which is primary in systems other than hemopoietic.

W. W.

THE ENDEAVOR OF JEAN FERNEL. With a List of the Editions of His Writings. By SIR CHARLES SHERRINGTON, O.M. Pp. 223; 27 ills. Cambridge: University Press, 1946. Price, $3.50.

THIS book, which had its origin in a Vicary Lecture given by its distinguished author, deals with the outstanding reform of medicine of the 16th century accomplished by the most learned physician of his time, "one of the relatively few who as they enter advanced years grow more modern." The same statement might be made about the author of this book, who has brought to it a freshness of material, point of view and diction that might well be emulated by younger writers.

Fernel's *De Naturale Parte Medicinae* (1542) is named by Sherrington as the first separate treatise on physiology composed in 13 centuries, *i. e.*, since Galen's *De Usu Partium*. Written, however, 80 years before Harvey's discovery of the circulation of the blood, and without benefit of chemistry or microscope, it treats of such matters as the Elements, Temperaments, Humours, and so on; and, as Fernel himself observes, "in passing from anatomy to physiology . . . we pass from what we can see and feel to what is known only by meditation." In his late fifties, while conducting a huge practice, Fernel composed *Medicina* (1554) (published also posthumously, 1567, as *Universa Medicina*). This is part of what was a never-to-be-completed system of medicine and consists of the *De Naturali* (here called Physiologia), *Pathologia*, and *Therapeutica*. The Pathology, Fernel's best known book, has been highly and deservedly praised. Various printed portraits of Fernel are discussed in the text and in Note XI; his full-length portrait on the title page of the 1657 Elzevir Celsus might well have been included.

The list of editions of Fernel's writings and the biographic notices, which include a translation from the Latin of Plancy's Life, complete this admirable production, which offers in unusually pleasant form an entertaining picture of 16th century French science as well as a sympathetic tribute from an old admirer to a great physician and "modern man."

E. K.

THE MODERN TREATMENT OF DIABETES MELLITUS. By WILLIAM S. COLLENS, M.D., Chief of the Diabetic Clinic and Clinic for Peripheral Vascular Diseases and Associate Visiting Physician, Israel Zion Hospital, Brooklyn, etc.; and LOUIS C. BOAS, M.D., Assistant in the Diabetic Clinic and Clinic for Peripheral Vascular Diseases, Israel Zion Hospital, etc. Pp. 514; 193 figs. Springfield, Ill.: C. C Thomas, 1946. Price, $8.50.

DIABETES. By HENRY J. JOHN, M.D., F.A.C.P., LT. COL., M.C. With a Foreword by DR. WILLIAM S. MIDDLETON. Pp. 300; 74 figs. St. Louis: C. V. Mosby, 1946. Price, $3.25.

BOTH monographs aim to guide the physician in the management of diabetes mellitus. Differences in procedure are apparent. As examples: the usefulness of postprandial blood sugars is overlooked by Drs. Collens and Boas but is emphasized by Dr. John. The former employ glycosuria, and particularly the quantitative urinary excretion of glucose, as a basic guide to treatment. The latter discusses quantitative glycosuria adequately but so briefly that it is obscured by his emphasis on the blood sugar in the adjustment of treatments. There are, of course, numerous items in both volumes which will evoke marginal pencilling by some readers; but these details should not obscure the fact that both books are satisfactory guides to the diagnosis and treatment of diabetes. In both, much of the language is that which the physician will use to instruct patients and both contain the usual diet lists, tables of body weight, etc.

In the monograph by Drs. Collens and Boas, the use of the glucose equivalent of insulin as a means of estimating the dose of insulin is adequately counteracted by their detailed directions for the follow-up observation of patients. Their series of chapters in which the treatment is related to the severity of diabetes and the type of patient

comprises one of the best presentations of practical management that has been made. The chapter on juvenile diabetes is good. The chapters on the complications of diabetes are concerned primarily with the influence of these complications on treatment and are not sources of statistical information. The chapters on peripheral arteriosclerosis present a practical summary of the methods of diagnosis and treatment used in today's vascular clinics. Finally the headings, outline and format are such that they should make this volume convenient for rapid reference.

In Dr. John's manual, the hypothesis that hyperglycemia from any cause may produce injury of the islands of Langerhans is accepted as the basis for the accurate control of diabetes by means of blood sugar determinations. There are no directions for the technique of insulin administration, which physicians know anyhow. The outline format is lacking. The text covers most of the problems of diabetes which confront physicians and supplies concise answers from the author's large experience. The charts and case reports provide a compendium of contributions. The chapter on diabetes in children is especially good, and the collection of "do's and dont's" condenses some of the wisdom, aphorism and enthusiasm which permeate this book.

In summary, both of these monographs may be recommended. The differences in style, arrangement and viewpoint supply physicians with a choice of counsel for a single purpose, namely, good care of the diabetic.

F. L.

SKIN DISEASES, NUTRITION AND METABOLISM. By ERICH URBACH (collab. EDWARD B. LEWINN), Associate in Dermatology, University of Pennsylvania. Pp. 597; 266 ills.; 112 tables. New York: Grune & Stratton, 1946. Price, $10.00.

THE importance of food in maintaining a balance of well-being and the use of diets to correct disease are ancient but sound conceptions. This rationale and elaboration have developed through extensive research in the physiology and chemistry of metabolism, with a literature now voluminous. Urbach has carefully catalogued the progress to date and together with his own investigations has produced a manual on the effect of food on the body in health and disease. While the main thesis is concerned with the effects on the skin, the volume holds much of interest to the internist, the allergist, the dietitian and the physiologist. The sections on nutritional causes and nutritional therapy of skin diseases are compact but complete and will be greatly welcomed by anyone who has had to deal with such refractory conditions as the various forms of eczema, the acnes, urticaria and the increased number of recognizable vitamin deficiencies. In addition, there are sections on the influence of nutrition on the physiology of the skin, diet in metabolism, food allergies and the relationship of internal disease and the skin. The inclusion of a variety of tables, and practical illustrative diets, adds greatly. The illustrations are well chosen, and the entire format is excellent. An index of subjects and index of authors are included.

R. G.

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